The Nation's Investment in Cancer Research
A Plan and Budget Proposal for Fiscal Year 2002

Review Draft
July 2000

Reviewers are asked to submit comments and suggestions on this document to:

Office of Science Planning and Assessment
National Cancer Institute
National Institutes of Health
Building 31, Room 11A03
31 Center Drive
Bethesda MD 20892-2590

If you have questions, please contact:

Cherie Nichols at 301/496-5515,
nicholsc@mail.nih.gov
or
Kathie Reed at 301/435-5163,
reedk@mail.nih.gov

The Nation's Investment in Cancer Research
NCI's Plan and Budget Proposal for Fiscal Year 2002

Contents

* To be added.

Executive Summary

The National Cancer Institute (NCI) provides vision and leadership for our Nation's efforts to uncover the mysteries of cancer and ensure that research results are converted into better care for people with cancer and those at risk for cancer. Key to the success of this mission is planning to ensure that we take advantage of opportunities that hold the most promise, build upon what we have already accomplished, and optimize our ability to move research results to medical practice for the benefit of every cancer patient.

Through groundbreaking research in cancer biology, causation, prevention, detection, treatment, and survivorship, NCI is moving science forward toward our ultimate goal to prevent or cure all cancers. In Fiscal Year 2002 NCI will continue to implement plans in six "extraordinary scientific opportunity" areas and in several areas of special challenge that will ensure the continued high quality of cancer research and facilitate the application of research results in the clinic. NCI will also continue developing and implementing national research agendas to ensure the fastest possible progress in preventing and curing specific forms of cancer.

Progress in Our Fight Against Cancer

In the final years of the 20th century, we have seen an explosion of progress against cancer. The revolution in molecular biology has brought us a fuller understanding of how molecular changes in the human body, often coupled with environmental and lifestyle factors such as diet and exercise, may give rise to cancer. New molecular technologies are enabling us to identify features of individual cells in ways unimagined even 10 years ago. More standardized and comprehensive clinical, epidemiologic, and pathologic data, as well as the controlled collection, storage, and analysis of biospecimens have greatly enhanced the information available to scientists working to identify the causes, prevention, and cure for cancer. Similarly, advances in imaging technology are vastly improving our ability to detect and evaluate tumors, select appropriate treatments, monitor treatment effectiveness, and assess prognosis.

Cancer incidence and mortality statistics tell us that our continued investments in basic, clinical, and population research and related technologies are beginning to pay off. The rate of new cancer cases declined on average 1.3 percent per year from 1992 to 1997. The cancer death rate decreased 0.6 percent per year between 1991 and 1995 and 1.7 percent per year from 1995 to 1997. Yet, even though many people with cancer are living longer and with a better quality of life, cancer remains a major public health problem and perhaps the most feared of diseases. Moreover, the burden of cancer is not borne equally by all population groups in the United States and the quality of cancer care varies considerably.

Planning Our Course for Fiscal Year 2002

To continue to push toward our ultimate goal of preventing or curing all forms of cancer for all people, NCI will:

- Sustain at full measure our proven, productive research programs.
- Seize the extraordinary scientific opportunities in broad research areas.
- Build our capacity for the future and address issues of special concern to the cause of cancer.

We also work to plan and implement national agendas for disease-specific research as part of our ongoing process of building upon broadly applicable research areas and capabilities to address the specific research needs of the more than 100 specific types of cancer.

Sustaining Proven, Productive Research Programs

Science cannot thrive – indeed, it cannot even take place – without the resources that support an enterprise of discovery. As the Federal focal point for cancer research, NCI conducts, coordinates, and funds cancer research through its Extramural and Intramural Research Programs (ERP and IRP). The ERP supports individual basic, clinical, and population scientists; centers; a host of collaborative research teams operating within a variety of networks and consortia; a comprehensive cancer control program; and training, education and career development activities. NCI's strong clinical research infrastructure includes a comprehensive program of clinical trials in cancer treatment, early detection, and prevention. NCI's Cancer Centers, Cooperative Groups, and Community Clinical Oncology Program are where findings from the laboratory are translated into new treatments, diagnostic tools, and preventive interventions. About 73 percent of the Institute's budget supports basic and clinical studies conducted through the ERP by researchers and clinicians across the Nation.

The IRP, representing approximately 16 percent of the Institute's budget, supports over 400 (Check number) principal investigators in NCI's Divisions of Cancer Epidemiology and Genetics, Basic Sciences, and Clinical Sciences, and is organized to complement ongoing research in universities and industry. It is uniquely structured to address cancer research problems whose resolution requires long-term commitments and that may be considered unsuitable for extramural funding mechanisms. The IRP has been involved in pivotal discoveries in cancer research, such as the first successful treatments for childhood leukemias, establishing the foundations for tumor vaccines, and identifying genetic causes for familial cancers.

Seizing Extraordinary Scientific and Technologic Opportunities

Six areas of extraordinary scientific opportunity in cancer research are continued from Fiscal Year 2001 into this 2002 Plan and Budget Request. Identified through formal input from cancer scientists, educators, advocates, and community leaders, these areas are *Genes and the Environment; Cancer Imaging; Defining the Signatures of Cancer Cells: Detection, Diagnosis, and Therapy; Molecular Targets of Prevention and Treatment, Research on Tobacco and Tobacco-Related Cancers, and Cancer Communications.*

Genes and the Environment

Our understanding of the causes and extent of molecular changes that lead to cancer has grown by studying how lifestyle and other environmental factors interact with individual genetic susceptibility. Research in this area is critical to our understanding both of how environmental

exposures influence molecular changes and why some people exposed to cancer-causing agents in the environment develop cancer and others do not. For example, why does one person exposed to tobacco smoke or the human papillomavirus develop cancer while another does not? Why do a population's cancer rates often change after its members migrate from one country to another? NCI's goal in this important research area is to discover genetic, environmental, and lifestyle factors, and their interactions, that define cancer risk and use this information to inform the development of new strategies for prevention, early detection and treatment. We will achieve this goal through research on environmental risk factors, susceptibility genes, and their interactions; development of risk models to integrate genetic and environmental determinants of cancer; and clinical studies to address the clinical, behavioral, and societal issues associated with cancer susceptibility.

Cancer Imaging

Advances in imaging technology are allowing us to view physiological, cellular, and molecular processes in living tissue. Through such "functional imaging," we can see processes like blood flow, oxygen consumption, or glucose metabolism in real time as they take place in living cells of the body. Cellular and molecular imaging promises to be a key tool in translating this knowledge into better ways of diagnosing, treating, and preventing disease. To ensure continued exploration of the benefits of imaging technology in cancer, NCI will accelerate the discovery and development of imaging methods and use these new technologies to identify the biological and molecular properties of precancerous and cancerous cells in order to predict clinical course and response to interventions. Continued imaging technology development will enable us to combine imaging techniques with radiation sources and high performance computing to more precisely target radiation treatments to a tumor's three-dimensional contours, sparing surrounding normal tissue. Parallel developments in image enhancement agents will continue to improve our ability to capture changes in the biochemical makeup of cells and other living structures. These developments will lead to a whole range of improved cancer prevention, diagnostic, and treatment options.

Defining the Signatures of Cancer Cells: Detection, Diagnosis, and Therapy

New molecular-based technologies are enabling us to identify the features of individual cells in ways inconceivable to our scientific predecessors. All cells have unique, identifiable "signatures"– a combination of active and inactive genes, and the proteins and other cellular products being manufactured by the cell. New technologies are enabling us to read and understand these signatures and to detect signature changes that signal the presence of cancer. By reading cellular signatures accurately, we may be able to detect and diagnose very early cancers, before they invade nearby tissues. In fact, with the tools we are developing, a single drop of blood from a patient's finger may be all that will be needed to determine the presence of cancer, assess the threat it poses by comparing its traits to profiles in an online library of tumor characteristics, choose the best possible treatment, and monitor a patient's recovery. NCI's goal in this area of extraordinary opportunity is to generate a complete catalog of distinguishing molecular signatures of normal, precancerous, and cancer cells at all stages and in all tissues, and use the catalog to develop diagnostic techniques for the earliest detection of precancerous lesions and cancers. With this information we can develop signature-based therapies, identify subsets of patients with different prognoses, and predict therapeutic response.

Molecular Targets of Prevention and Treatment

Many of our existing anti-cancer compounds inhibit the growth of cancer cells successfully, but they also affect healthy cells, causing short- and long-term toxic effects that can themselves endanger patients' health and quality of life. As molecular biology has advanced, new technologies have emerged, and our knowledge has grown about the nature of cancer cells and molecular changes that occur during tumor development, we are now positioned to develop a whole new generation of cancer treatments and preventives that attack essential tumor cell processes with greatly reduced side effects. NCI will build on the convergence of advances in cancer biology, synthetic chemistry, biosynthetic chemistry, high throughput screening and molecular and functional imaging to accelerate the discovery, development, and testing of prevention and treatment agents that target the molecular changes underlying various stages of cancer initiation and progression.

Research on Tobacco and Tobacco-Related Cancers

An estimated 450,000 people in the United States will die this year alone from tobacco-related diseases – the most preventable and costly cause of death in our Nation. The global picture is even more sobering: more than a billion people smoke worldwide and an estimated three million die annually from tobacco-related illness. Clearly, tobacco – whether in cigarettes, cigars, pipes, or smokeless products – poses an extremely serious threat to health. Using tobacco significantly increases a person's risk of lung, mouth, pharynx, larynx, esophagus, pancreas, cervix, kidney, and bladder cancers, as well as heart disease and many other conditions. We know that people who stop smoking, regardless of age, live longer than those who continue to smoke, although their risk for lung cancer remains somewhat higher than if they never had smoked. To respond to this urgent threat to life and health, NCI has identified research on tobacco and tobacco-related cancers as an area of extraordinary opportunity for increased investment.

Over the past 30 years, we have learned much about the enormous burden tobacco use places on our Nation's public health. We understand far better the molecular factors that underlie a cell's transformation from normal to cancerous following exposure to tobacco carcinogens, and scientists have identified many cancer-causing agents contained in tobacco smoke. Evidence indicates that genes interact with environmental factors to influence whether an individual will start smoking, how early he or she will start, and how difficult it will be for him or her to quit. We also have learned a great deal about the psychosocial, biobehavioral, and biological determinants of tobacco use and addiction. NCI will now build upon this knowledge base and devote increased resources to further understand the specific causes of tobacco use, addiction, and tobacco-related cancers and apply this knowledge to their prevention and treatment, particularly in high-risk individuals and groups.

Cancer Communications

The current communications revolution, particularly the power and potential of the Internet, is unprecedented in human history. At no other time has it been so easy for so many people to access such a vast wealth of information. NCI has committed to use the new media and refined health communication theories to empower people to make informed cancer-related decisions and to engage in behaviors that will improve their health. To date, we have been able to apply our increased understanding of communications to interventions that have positively influenced

smoking rates, dietary habits, and screening practices that are reducing cancer risk in many populations. But despite our successes, major gaps remain in our knowledge and understanding of how consumers use health information and how to ensure that major segments of the population have access to the array of cancer communications media. Both the public and the physician community have a great need for timely, accurate cancer-related information on topics ranging from primary prevention to survivorship and end of life issues. This information must accommodate the diverse languages, literacy levels, cultures, locales, and technological resources of our population. In pursuing this extraordinary opportunity, NCI's goal is to increase our knowledge about, tools for, access to, and use of cancer communications by the public, patients, survivors, and health professionals – with a special focus on diverse populations – to accelerate reductions in the U.S. cancer burden.

Building Capacity for the Future

Recent advances in science and technology are truly astounding. In the summer of 2000, the first draft of the entire map of the human genome was unveiled. More than a thousand researchers from six nations revealed nearly all three billion letters of the human genetic code. This achievement has profound implications for cancer research – as we discover the functions of these genes and the proteins they produce, we will be able to convert this knowledge into cancer prevention and treatment options to reduce, and some day ameliorate, the burden of cancer. However, it should be recognized that mapping the genome could not have been accomplished without sustained resources and collaborations among biologists, chemists, physicists, engineers, mathematicians and computer scientists. Similarly, major breakthroughs in cancer research depend on building and sustaining the strong research infrastructures and interdisciplinary collaborations that will enable us to apply rapidly evolving discoveries in cancer genetics, cancer biology, molecular-based technologies, new and enhanced imaging tools, and the new targeted therapeutic interventions. NCI's role is to provide the vision, creative environments, and diverse resources needed to ensure a smooth flow between accelerating cancer research advances and the their application in interventions to prevent and treat cancer, and meet the supportive care needs of people with cancer.

To respond to this challenge, NCI has identified eight key areas requiring increased investment: *Investigator-Initiated Research; Centers, Networks and Consortia; National Clinical Trials Program; Informatics and Information Flow; Studying Emerging Trends in Cancer; Training, Education, and Career Development; Quality of Cancer Care; and Reducing Cancer-Related Health Disparities.*

Investigator-Initiated Research

Investigator-initiated research – research conceived and conducted by scientists in laboratories and clinics across the country and at NCI – is the well spring of scientific discovery. Funded and sustained by a variety of NCI grant mechanisms, our investigator-initiated research is continually yielding discoveries and insights into the mechanisms and causes of cancer and its prevention, detection, diagnosis, treatment, control, and survival. NCI's role is to support the exploration of new leads across the cancer research continuum. This includes expanding our research portfolio to include a greater number of research proposals that may be somewhat risky, highly speculative, or that pursue novel paths. We also must continue to expand the translational

research that converts basic science discoveries into practical, affordable, and effective ways of restoring cancer patients to health and preventing cancer in all populations. In addition, we must invest in areas identified by disease-specific Progress Review Groups (PRGs), NCI advisory committees, and NCI staff that present unique opportunities or needs. Our goal for FY 2002 is to speed the rate of discovery and accelerate application of those discoveries to the population by expanding and facilitating researchers' access to resources and new technologies.

Centers, Networks and Consortia

NCI's challenge is to create and sustain integrated research environments that foster the complex multidisciplinary interactions needed to address the "big picture" problems in cancer research. These integrated research environments must functionally link basic, clinical, population, and behavioral scientists to each other and to newly developing, diverse fields of science and technology. Access to many different patients and at-risk populations, tissue banks, new technologies, and state-of-the-art informatics is critical to advances in cancer research. To address this need, NCI will create and sustain research infrastructures for collaboration, technology support and development, and access to resources that enable multiple scientific disciplines to address large problems in cancer that could not be solved by individual investigators. This goal will be achieved by expanding our nationwide infrastructure of NCI-designated Cancer Centers, Centers of Research Excellence, Networks, and Consortia in ways that promote and facilitate complex scientific interactions, provide critical research resources, and foster the exchange of information and ideas through new communication linkages.

National Clinical Trials Program

The research investment of the past decade has led to major advances in our understanding of tumor biology and potential molecular targets for cancer prevention and treatment. It also has resulted in a dramatic increase in the number of new preventive, diagnostic, and therapeutic agents ready to be tested in clinical trials. However, the number of agents that will merit testing in people is outstripping our capacity to test them in a trial setting. Simply put, our present clinical trials system is failing to keep pace with discovery. This is particularly true for Phase III trials, the final crucial step in translating discoveries into new treatments and prevention strategies for patients. Presently, NCI and its grantees are able to initiate only about 30 Phase III trials each year, a problem compounded by the fact that only about 20,000 patients enter Phase III trials annually. A variety of reasons contribute to this low number, including limited access to trials, lack of insurance coverage, patient-physician communication issues, and therapy choice. NCI's challenge is to ensure that the Nation's cancer clinical trials program is poised to address the most important medical scientific questions in cancer treatment and prevention quickly and effectively through state-of-the-art trials that are broadly accessible to cancer patients, populations at risk for cancer, and physicians who care for them. To meet this challenge, we will increase new agent development and testing, increase participation in trials, and improve access to treatment and prevention trials to help reduce outcome disparities in special populations.

Informatics and Information Flow

Patients and medical researchers around the world are benefiting from the explosive growth of the Internet and advances in computing and information technology. But with this vast amount of information and improved access to it comes a very real need for a system to analyze, organize, share, and apply material from diverse sources in an efficient and timely way. NCI has taken on

the challenge to develop a knowledge management framework that will unify the research, cancer practice, and patient communities. Specifically, NCI will create a Cancer Informatics Infrastructure (CII) that enables cancer research by enhancing information and resource exchange among researchers, clinicians, and the public and reduces the barriers experienced by individuals seeking information about cancer prevention, diagnosis, and treatment. The first step in this endeavor is to create a framework to increase the speed with which we carry out clinical trials in cancer prevention, diagnosis, and treatment. To increase the speed, efficiency, and accuracy of reporting clinical trials results, a revised system for reporting all data collected during a clinical trial has been developed and common forms, terminology, and reporting requirements are being created. NCI will now expand this infrastructure to enable integration and interface among research initiatives of all types, improve information access for all user communities, and improve access to informatics tools.

Studying Emerging Trends In Cancer

A vital mission of the NCI is to monitor the national cancer burden through incidence, morbidity, mortality, and survival statistics and to evaluate the impact of cancer-related risk factors, health behaviors, and health services on the cancer rates and trends observed in various parts of our population. Since 1973, the Surveillance Epidemiology, and End Results (SEER) cancer registry program has been the mainstay of NCI's cancer surveillance effort. Recent changes in health care financing, information and computer technologies, and the social and cultural diversity of our country now present new challenges and opportunities in surveillance research. Our understanding of how risk factors, screening, and treatment may affect trends in cancer is beginning to unfold, and advancing knowledge in these areas will require new data sources and statistical methods. In addition to traditional incidence, survival, and mortality data, we need data on patterns of care, patient-centered measures such as quality of life, and sociodemographic and economic population characteristics. New investments also are required to support and adopt new methodologic and informatics tools, such as new approaches to modeling trends, more refined cancer maps, and geographic information systems that allow data linkage and statistical analysis of individuals and potential environmental exposures by location. NCI's goal is to expand current surveillance data systems, methods, communications, and training to improve capacity for monitoring progress in cancer control and to more fully explore potential causes of cancer nationally and among diverse populations.

Training, Education, and Career Development

Training, education, and career development for the next generation of scientists remains one of our most important challenges. The scientists of the future will need to be highly versatile in their use of new technologies; able to work in teams to understand the complex environmental, genetic, and molecular variables contributing to human cancers; and better prepared to translate discoveries into public benefit. It is critical that we implement training, education, and career development strategies to address five crucial issues: We must more adequately prepare basic scientists by encouraging them to conduct research directly related to human cancer, and preparing them to collaborate with clinical and population scientists and function in team research settings. We must reverse the migration of medical doctors from research to practice by ensuring that clinical investigators have protected time to conduct patient-oriented research. We must increase the numbers and stabilize the careers of population, behavioral, and public health scientists. We must create a research workforce that is ethnically and racially diverse, and we

must attract and integrate a wide array of technical and informatics disciplines into cancer research. NCI will design and implement opportunities for scientists at all career levels to meet the challenge of building a stable, racially and ethnically diverse cadre of basic, clinical behavioral, and population scientists trained to work together effectively and use the most advanced technologies to build our knowledge base and translate discoveries into more effective cancer prevention, detection, diagnosis, and treatment strategies.

Quality of Cancer Care

More than eight million Americans will be treated for cancer in 2000, with 1.2 million having newly diagnosed cases. We have known for some time that the quality of cancer care varies among the geographic regions and populations that make up our Nation. NCI, which has long been at the forefront of basic and clinical research to understand the causes of cancer and translate these findings into treatments, now proposes an ambitious program of research to improve the quality of cancer care by strengthening the information base for cancer care decision making. The aim is to better understand what constitutes *quality* cancer care, with an emphasis on the patient's perspective; to identify geographic, racial/ethnic, and other disparities in who receives quality care; and to strengthen the scientific basis for selecting appropriate interventions along the entire continuum of care from prevention through end of life care or survivorship. Therefore, NCI's goal in meeting this challenge is to enhance the state of the science for defining, monitoring, and improving the quality of cancer care and ensure that Federal-level decision making, in particular, on cancer care delivery, coverage, and regulation is informed by the best available scientific evidence.

Reducing Cancer-Related Health Disparities

Advances in biomedical science have contributed to increased longevity and improved quality of life for many Americans, but the burden of disease is not borne equally by all population groups in the United States. Marked disparities in cancer incidence and mortality exist between men and women, and among our racial and ethnic populations. Regardless of racial or ethnic group, persons of low socioeconomic status have higher death rates for most cancers than persons of higher socioeconomic status. Human life circumstances, which include social position, economic status, culture, and environment, are critical determinants of who is born healthy, who grows up healthy, who sustains health throughout their life span, who survives disease, and who maintains a good quality of life after diagnosis and treatment. In particular, social injustice, through its impact on absolute and relative poverty, racial/ethnic discrimination, risk-promoting lifestyles, and environmental exposures, has to a large extent created the health disparities that currently exist in this country. NCI has embraced the challenge of understanding the causes of health disparities in cancer and developing effective interventions aimed at reducing or eliminating these disparities. We will increase fundamental research into the social causes of health disparities, the psychosocial factors that mediate them, and the biologic pathways that can explain their impact. In addition, we will expand cancer control intervention and population research on disparities, better define and monitor cancer-related health disparities, and strengthen training and education in this research area.

This plan and budget represent an investment in cancer research and the infrastructures that must exist for research to take place. More importantly, however, this document describes our

proposal for investing in the Nation's health and hastening the day when cancers are easily prevented and cured and the fear of cancer is finally lifted.

Planning National Agendas for Disease-Specific Research

Effective planning is integral to NCI's efforts and crucial to scientific progress. Planning involves identifying needs and opportunities, setting priorities, developing strategies for implementing decisions and recommendations, and making sure that a reliable infrastructure supports all of our initiatives. To help develop an optimal national research agenda for specific types of cancer, the Institute seeks advice through Progress Review Groups (PRGs). PRGs are small panels of experts convened to assess the state of the science and NCI's current research portfolio for a particular cancer, identify gaps in current knowledge and barriers to progress, and recommend future research directions and related actions. The PRGs have proven to be a highly successful and important part of NCI's planning process.

Introduction

Planning, funding, and operating crucial research programs is an exceedingly complex endeavor. Each year, as mandated by the National Cancer Act of 1971 (P.L. 92-218), the National Cancer Institute prepares a detailed plan to build upon our research successes and provide the technologies and resources needed to support our scientific workforce, overcome barriers to new knowledge, and hasten the day that our ultimate goal is realized: the prevention or cure of all cancers. This annual plan and budget request – communicating the Institute's needs and plans – is provided directly to the President of the United States in the Fall of each year as he formulates his budget request to the Congress for the entire Federal government and more specifically, for cancer research.

This document is our plan and budget proposal for Fiscal Year 2002. Though not a comprehensive discussion of all of NCI's activities, it describes research efforts to improve our understanding of and care for each of the more than 100 types of cancer, as well as the essential basic research that leads to findings that may be applicable to several cancers. In addition, this plan addresses other issues of special concern in our fight against cancer, such as the quality of cancer care, and disparities in access to information, patient care, and research opportunities and careers. The document includes:

- **NCI's 2002 Budget Proposal –** the resources needed to support our core activities, Extraordinary Opportunities, and Challenge areas

- **Highlights of Progress** – a synopsis of particularly important advances over the past year in science and technology, and recent changes in NCI's infrastructure and organization that are paving the way for tomorrow's discoveries

- **NCI's Role in Cancer Research** – an overview of NCI's mission and our approach to providing vision and leadership to the cancer research community

- **How We Carry Out Our Role** – a description of NCI's planning, priority-setting, and assessment activities, advisory and liaison activities that provide guidance to the Institute, and NCI's core research programs and infrastructure

- **Planning National Agendas in Disease-Specific Research –** a description of a unique planning mechanism through which NCI works with the research and advocacy communities to chart the course of research for specific cancers

- **Extraordinary Opportunities for Investment** – descriptions, plans, and resource requirements for six research areas for which NCI has determined that new, intensive efforts and increased resources have exceptional potential to yield profound insights into how cancer develops and lead to vast improvements in our ability to prevent, control, detect, diagnose, and treat cancer

- **NCI's Challenge: Building Our Capacity for Future Discovery –** descriptions, plans, and funding requirements for eight aspects of our crucial research infrastructure – the

resources, technologies, organization, and personnel without which progress cannot be achieved – that have been identified for special emphasis.

In addition, this document contains several **Spotlights on Research** focused on key research or other NCI activities of special interest this year. Two **People's Stories** highlight the struggles and the hopes of individuals dealing with cancer and the threat of cancer.

In addition to the President and the Congress, this document is intended for the use of NCI's research community including individual investigators, clinical and laboratory centers; the Institute's several advisory bodies; NCI staff; cancer information, education, and advocacy organizations; and public and private policymakers whose decisions affect cancer research and care in America. More than simply describing our plans and proposed budget, it is our hope that this document also will inform and inspire all those with a desire to see the burden of cancer finally lifted – researchers, care givers, and every individual – to join the fight against these devastating diseases.

NCI's Budget Proposal for Fiscal Year 2002

To be added.

Highlights of Progress

As we begin the new millennium, it is appropriate that we take stock of our progress – and lack of progress – against cancer and use this foundation of knowledge to chart our course for the coming years. We are making important progress against cancer, as is evidenced by continuing declines in cancer incidence and death rates. According to a new report by the National Cancer Institute, the American Cancer Society, the North American Association of Central Cancer Registries, and the Centers for Disease Control and Prevention, the rate of new cancer cases and deaths for all cancers combined declined between 1990 and 1997 in the United States. Although mortality rates are still increasing for some forms of cancer, including liver cancer and non-Hodgkin's lymphoma, death rates for the four major sites – lung, colorectal, breast, and prostate – continue to drop. These findings illustrate that, although our work is far from done, we are beginning to see the fruits of our Nation's investment in cancer research.

Still, scientific progress can move forward at a frustrating pace. Because advances in basic research, prevention, and treatment are incremental, it often takes years to see the cumulative effects of our efforts on populations at risk, patient survival, and improved quality of life. Moving from an insight to a tested successful intervention in people takes time, and there will always be a lag between our investment – the development of a solid knowledge base – and the payoff for a person with cancer or one at risk for the disease. Yet, every day, thanks to the dedicated efforts of cancer researchers and clinicians, we are making real progress toward our goal of overcoming cancer.

In the past few years, we have seen an explosion of progress against cancer. We have witnessed a number of important advances culminating from many years of intensive effort. We have begun to gather significant information from programs launched only two or three years ago. And, we have launched innovative new programs that will have far-reaching effects into this new century. The following – a snapshot of this recent progress – demonstrate how far we have come against cancer, and offer a glimpse of what is to come as we build on our successes to conquer cancer in a future that no longer is so distant.

Science and Technology Advances

Preventing Cancer/Cancer Control

Finding effective ways to prevent cancer has long been a central focus for NCI and cancer researchers. Prevention can take many forms, from smoking cessation and other behavioral changes to vaccines or antimicrobial agents against cancer-causing infections. And, with our increasing knowledge of the biology of cancer, we now have the promising new field of chemoprevention, which focuses on the development of man-made or identifying natural agents that interfere with the biological processes underlying cancer development.

Closely related to cancer prevention, cancer control encompasses research on the many diverse aspects of translating proven technologies and tested methodologies into routine practice in the community. For example, cancer control research may focus on identifying new ways to help

people stop smoking, or to encourage people to adopt a healthier diet, or to communicate health risks to certain population groups.

- NCI is collaborating with two pharmaceutical companies to study the **effectiveness of the drug, celecoxib, in preventing several precancerous and cancerous conditions**. An earlier NCI study determined that celecoxib helped reduce the number of colon polyps in patients with familial adenomatous polyposis (FAP), a condition which causes people to develop hundreds of thousands of colorectal polyps, a possible precursor to cancer. Based on this finding, the FDA approved celecoxib as an adjunct to usual care for patients with FAP. Now, NCI and its partners hope to determine whether celecoxib is effective in preventing sporadic polyps, hereditary nonpolyposis colon cancer syndrome (a medical condition that causes increased risk for early onset of colorectal and other cancers), Barrett's esophagus, bladder dysplasia, actinic keratoses and the progression of FAP to colorectal cancer.

- In a 32-month study in 14 Minnesota communities, seven "intervention communities" passed a **comprehensive youth access ordinance ensuring merchant compliance with tobacco age-of-sale laws** such as licensing fees, vendor penalties, clerk penalties, vending machine bans, self-service bans, purchaser penalties, and compliance checks. At the end of the study, daily smoking by youth in grades 8, 9, and 10 was reduced significantly in all seven intervention sites compared to those youth in the seven "control" communities that did not organize to change ordinances, policies, and practices. This study provides evidence that community policies to reduce youth access to tobacco can have a significant effect on youth smoking rates.

- Not all populations are affected equally by cancer. Yet, research is demonstrating that differences in cancer morbidity and mortality previously attributed to race are not due to supposed biological differences between populations or between the tumors individuals develop. Rather, these differences actually reflect the **too-frequent medical consequences of socially-defined race – socioeconomic status, educational level, and degree of access to high quality cancer care.** NCI-supported researchers recently compared the outcomes of black and white patients with colon cancer enrolled in five clinical trials. They found, as other analyses of NCI clinical trails have, that equal treatment yields equal outcome, and that race is not a factor in cancer-specific survival when there is equal treatment. Data from NCI's Black-White Study of Cancer Survival showed that compared with white women, black women with breast cancer (as well as poor women) were less likely to receive appropriate treatment after diagnosis. They also are more often diagnosed at a later stage of disease and are less likely to have a regular source of health care. Similar disparities in appropriate treatment have been demonstrated between various population groups with prostate, lung, and cervical cancers. NCI studies are now focusing on determining the reasons for the differences in care.

Detecting Cancer

New technologies that will enable us to detect and diagnose cancer early, before it has had a chance to spread, are on the horizon. Imaging devices and modalities are being developed and

tested that allow us to visualize the cell with greater precision than ever before. And, new methods for reading the signatures of cell are allowing us to identify the subtle differences between normal and cancer cells, and are leading us to the day when only a simple blood test is needed to detect cancer anywhere in the body.

- Preliminary findings from NCI's ASCUS/LSIL Triage Study (ALTS) have shown that **testing for the human papillomavirus (HPV), the primary cause of 90 percent of cervical cancers, is a highly sensitive way to detect the underlying abnormalities that may progress to cervical cancer**. The study's investigators questioned whether HPV testing might help physicians and patients decide how to handle the mildly abnormal and common PAP test result known as ASCUS (short for atypical squamous cells of undetermined significance). Although most of these mild abnormalities will go away without treatment, physicians have had no way to distinguish the less serious abnormalities from those that will progress to precancerous conditions or cancer. The ALTS investigators concluded that the HPV test effectively detects ASCUS lesions that need immediate attention. Scientists now are exploring ways to improve the test's specificity.

- Although early detection is the mainstay of successful cancer treatment, current non-invasive approaches for detecting small tumors have limited utility because they cannot distinguish small areas of abnormal cells from larger surrounding areas of normal tissue. Recently, however, scientists developed a new imaging method to more precisely image tumor cells, an important step toward non-invasive detection of small, and more treatable, tumors. In developing the method, the scientists injected tumor-bearing mice with a **unique imaging agent composed of near-infrared fluorescence imaging probes coupled with a novel substance that moves effectively into tumor cells**. When the agent was internalized into cancer cells, cellular enzymes "activated" the agent, causing it to fluoresce and allowing for non-invasive detection. The agent was not activated in non-tumor cells. Using this technique, the investigators were able to image tumors smaller than three-tenths of a millimeter in diameter. Although this new technique is still in the early stages of development, it shows great promise for the early detection of small tumors.

Treatment Advances

As recently as thirty years ago, when legislation launched the National Cancer Program, the idea of curing cancer seemed a remote ideal. This once-ideal is a now a reality for many cancers and within our grasp for others. Today, using insights gleaned from discoveries about cancer biology, we now are learning to tailor treatments for a specific cancer in a specific individual, to optimize the results of traditional treatments, and to target treatments to the cellular machinery of specific tumors. Our great hope is that targeted treatments will prove to be more effective and less toxic than our current approaches.

- Over the last 20 years, many cancer researchers have believed that immunotoxins hold great promise as a cancer treatment approach. The idea underlying this approach is elegantly simple: Bioengineer small antibodies, link them to a powerful toxin, and directly target and deliver deadly poisons to tumor cells. Yet, generating viable

immunotoxins has proven to be a significant challenge. A team of NCI scientists recently reported, however, that four out of four patients with hairy cell leukemia, an unusual cancer of immune B cells, responded to a **recombinant immunotoxin called LMB-2.** One patient has been in complete remission for nearly two years, and the other three patients had partial responses with significant reduction in the number of circulating malignant cells. All of the patients had not responded previously to standard treatments. As many as 25 percent of hairy cell leukemia patients develop a resistance to treatment, making this alternative potential treatment all the more promising.

- A new drug currently being developed jointly by NCI and the pharmaceutical company, Novartis, is producing promising results as a potential treatment for chronic myeloid leukemia (CML). Leukemia cells in nearly all patients with CML express an aberrant protein known as Bcr-Abl. The new drug, **STI571, targets leukemia cells by selectively** inhibiting **leukemia cells** that express this protein, making STI571 an promising candidate for development in the treatment of CML and other Bcr-Abl positive leukemias. Initial results from the Novartis-sponsored phase I study demonstrated that virtually all patients treated with STI571 (300 mg or more a day) had a complete hematologic response.

- Findings from a recent clinical trial showed that **13-cis-retinoic acid did not reduce the incidence of second cancers in patients with a history of early stage non-small cell lung cancer** who had been treated with surgery. In fact, in individuals who continued to smoke, the drug appeared to increase the risk of recurrence of the original lung cancer or of death compared to smokers taking only the placebo. Because this finding coincided with a protocol provision to stop the trial seven years after the first patient was enrolled, participants were told to stop taking their pills.

- **Thalidomide**, a drug used in the 1950s and 1960s as a sedative which led to birth defects in newborns of mothers who took the drug, **has now been shown to have clinical activity against Kaposi's sarcoma (KS), an AIDS-related cancer**. NCI researchers have shown in a phase II study that oral administration of thalidomide induced partial responses in 40 percent of the 20 patients treated. Thalidomide, which inhibits angiogenesis – the growth of new blood vessels to support tumor growth, brought about a 50 percent reduction in the number of KS lesions on the skin in eight patients while two others had stable disease and seven patients had progressive disease. The positive outcome of this trial warrants additional study of the drug. Thalidomide has also been shown, in early trials, to be active against multiple myeloma, a bone marrow disease.

- **A new anti-angiogenesis drug** being developed by NCI in collaboration with the pharmaceutical company Sugen **has shown activity against advanced colon cancer in an early clinical trial**. The drug, SU5416, targets vascular endothelial growth factor (VEGF), which is an essential signal for starting the process of angiogenesis. When used in combination with standard chemotherapy, SU5416 stopped cancer growth for an average of 9 and 1/2 months compared with six months for the usual therapy. Of the 28 patients on the phase I/II trial, 25 are still alive. Based on these promising results larger studies of the drug are being launched.

Understanding Cancer and its Causes

Progress in our understanding of the biology of cancer continues at an astonishing rate. We are learning more each day about how cancer arises from a single cell that behaves abnormally, dividing uncontrollably and eventually leading to the development of a tumor. We also are learning about the ways that genes, which direct the behavior of the cell, interact with a host of environmental agents to cause cellular malfunction and disease. Emerging new technologies are speeding our progress in cancer biology, enabling us to gather knowledge about the nature of cancer and providing critical insights into how we can prevent, detect, and treat this disease more effectively.

- **NCI-supported scientists have identified a genetic mutation that may be responsible for more than 11,000 of the 129,000 cases of colorectal cancer diagnosed annually in this country.** The TbetaR-I(6A) defect, a mutant form of the Transforming Growth Factor Beta (TGF-b) receptor, is a new mechanism – found in both cancer patients and healthy individuals – that may increase a person's risk for cancer. Comparing blood samples from cancer patients and healthy volunteers, the scientists observed the TbetaR-I(6A) mutation occurred more commonly in people with cancer than in healthy people, suggesting that the mutation may play a role in the disease. And, people who inherited a copy of the mutation from both parents, and thus carried two mutant copies of the gene, had the most pronounced risk for developing cancer. The scientists have suggested that this mutation may contribute to cancer's development, particularly colon cancer, by hampering a cell's normal efforts to control cell growth. This finding one day may help physicians identify at risk patients who should be followed closely for early signs of disease.

- Using the powerful, new DNA microarray technology, a team of scientists recently determined that the **most common form of non-Hodgkins lymphoma – diffuse large B-cell (DLCBL) – is actually two distinct disease.** This finding offers considerable insight into why only 40 percent of the 25,000 people diagnosed annually with this disease are cured with standard chemotherapy, while the majority relapse or die. The scientists created a novel microarray tool, which they labeled the "lymphochip", by threading more than 18,000 genes important to both lymphoid malignancies and the immune system onto a device similar to a computer chip. The lymphochip enabled them to rapidly compare gene activity of normal and cancerous B cells and generate gene expression profiles of the different cell types. After examining several different forms of non-Hodgkin's lymphoma (NHL), the scientists discovered that DLBCL showed two distinct patterns of gene expression, suggesting that this disease is actually *two subtypes* of NHL. This finding underscores the future importance of defining the distinct molecular characteristics of tumors as a path to more accurate diagnosis and targeted treatments.

- NCI researchers have found that **women who use combined estrogen-progestin replacement therapy have a greater risk for developing breast cancer than those who use estrogen alone.** Using 15 years of follow-up data from 46,000 women who

participated in the Breast Cancer Detection Demonstration Project (BCDDP) -- a nationwide breast cancer screening program – the scientists found that compared to non-users, the relative risk for breast cancer increased by 8 percent per year for the estrogen-progestin therapy compared to 1 percent for estrogen therapy alone in women who had used hormones during the previous four years. There was no increase in risk among women who had stopped either therapy for more than four years. Although the increase in risk is still low for women taking both hormones, it further complicates the decision women face about whether to take hormone replacement therapy to ease the symptoms or reduce some of the health concerns associated with menopause.

Charting Our Future

NCI's mission to conquer cancer – to lessen the burden of this disease on present and future generations – is the driving force behind the Institute's diverse research programs and activities. Planning for a future free of the fear of cancer requires charting a course that not only embraces our growing body of knowledge about cancer, but a course that challenges the research community to go beyond business as usual and develop initiatives, programs, and even new partnerships to use new discoveries, exploit scientific opportunities, and apply emerging technologies in the prevention, detection, treatment and control of cancer.

NCI has spent much time and effort developing and supporting an infrastructure that sustains the research programs that today are enabling us to pursue a path of scientific excellence and discovery in cancer research. And, we have established a long tradition of seeking better ways to inform the process of identifying needs and opportunities in the cancer field, setting priorities, and implementing decisions and recommendations that lead to new research initiatives and programs, and improve existing ones.

- Over the past three years, NCI has assembled **Progress Review Groups (PRGs),** composed of researchers, health professionals, industry representatives, and lay advocates, to assess the state of our knowledge, identify scientific opportunity and need, and chart a course for future study. To date, PRGs have been completed for breast, prostate, and colorectal cancers. A Brain Tumor PRG, conducted in collaboration with the National Institute of Neurological Disorders and Stroke, is nearing completion. Ongoing and planned PRGs are outlined in the chart on page xx. With three PRGs complete, and more soon to be completed, the NCI has begun to take stock of the success of the PRGs in supporting and promoting disease-specific research. Through our analytic mapping exercises, we've found that about 80 percent of the PRGs' recommendations map to programs that are already in place, or to programs that can be modified to address the recommendations. In fact, there are core scientific needs – for example, the need for research training, or for the development of biomarkers of disease – that appear to be universal, regardless of the disease. A certain percentage of recommendations represent genuine gaps in the research or the infrastructure that the NCI must and will address.

- The NCI **Strategic Plan to Reduce Health Disparities** is part of a major national commitment to identify and address the underlying causes of disease and disability in

racial and ethnic communities throughout the country. Because these communities carry an unequal burden of cancer-related health disparities, NCI recognizes the need to greatly enhance our research, education, and training programs that target these pockets of need. From cancer prevention to clinical trials recruitment to cancer survivorship, the Strategic Plan will help us understand the causes behind health disparities in cancer and to develop the most effective and culturally sensitive ways to work with underserved communities to eliminate these disparities. In addition, NCI has named an **Associate Director for Health Disparities** and has convened a **Special Populations Working Group** to bring the expertise of individuals in the community to bear in assessing the research questions that should be addressed.

- The quality of cancer care is a major national concern and NCI is responding with a quality of care initiative to address the concern. In presenting an initial design of the research program to DHHS Secretary Donna Shalala, NCI urged that cancer be made a "working model" for quality of care research and application. The Secretary responded by approving the creation of the **Quality of Cancer Care Committee**, a trans-agency task force with representatives from Federal agencies involved in cancer care delivery, coverage, and regulation. In addition, NCI's quality of care initiative operates organizationally within the Secretary's larger Quality Improvement Initiative.

- Effective communication is crucial element in all of NCI's activities. Recognizing the importance of this tool, **NCI restructured and realigned its three existing communications offices into one NCI Office of Communications**. The reorganization will enable the Institute to integrate our communications activities throughout the Institute, provide the infrastructure to facilitate these activities by incorporating new technologies, and enhance our ability to communicate the importance and achievements of cancer research to the Nation.

- Innovations and advances in the field of cancer research have often come about through collaborations, the sharing of resources and technologies, and the bringing together of knowledge and expertise from several disciplines and related fields. Recognizing the tremendous benefits of collaborations, NCI is forging partnerships to encourage collaborations across scientific disciplines, with other government agencies, and among academic, research, and industry organizations and scientists. Examples of such partnerships include a **collaboration with NASA to develop minimally invasive molecular biosensors.** The two agencies host a web-based technology forum designed to bring together a diverse group of scientists, technologists, and engineers into a common technology development environment. NCI also participates in a number of **Cooperative Research and Development Agreements (CRADA)** with industry partners CRADAS have been instrumental in producing important anti-cancer agents, such as Taxol. And, through a CRADA with an industry partner, NCI is planning to conduct clinical trials of decitabine, a promising new anti-cancer drug that may have a role in combating a number of solid tumors and blood cancers. Finally, NCI has joined with other NIH institutes in an NIH-wide **Bioengineering Consortium (BECON)** to focus on bioengineering issues and foster new understandings collaborations, and

transdisciplinary initiatives among the biological, medical, physical, engineering, and computational sciences.

Foundations for Future Discovery

To conquer cancer, NCI must not only pursue new knowledge, but establish foundations for future discovery that ensure we have the trained scientists, the technologies, and the necessary infrastructure ready to take our knowledge and apply it to reducing the burden of cancer. Important components of our foundation for discovery were launched or enhanced this year.

- To develop new potential anti-cancer agents NCI launched the **Rapid Access to Intervention Development** (RAID) program. Designed to efficiently move novel, scientifically meritorious treatment interventions developed in academic settings into the clinic, this ambitious program funded 14 projects in 1999 and 2000. Because academic institutions commonly lack the capacity to develop drugs, promising ideas and candidate molecules cannot always move forward in the drug discovery process. RAID places NCI's drug development resources at the service of investigators with molecules that hold promise for cancer treatment. By providing the resources needed for preclinical development of drugs and biological agents, this program removes the most common barriers between laboratory discovery and clinical testing.

- When the **Phased Innovation Award** was launched to support technology research from the evolution of an innovative concept, through feasibility testing, to subsequent full-scale development, it was an immediate success. With funding for full-scale development dependent upon successful feasibility testing, researchers responded with more unique concepts and lag time between review process and application funding has been significantly reduced. Now NCI is expanding the use of this award to generate research opportunities in other areas, such as biomedical imaging. This mechanism has also gained the attention of other NIH Institutes who may adopt this grant mechanism.

- Designed to rapidly address emerging scientific opportunities **Centers of Excellence** are composed of multidisciplinary and translational research teams focused on a specific disease, modality, biologic process, or scientific area of interest. In addition to Specialized Programs of Research Excellence – our first Centers – Transdisciplinary Tobacco Use Research Centers, *In vivo* Cellular and Molecular Imaging Centers, and Interdisciplinary Research Teams for Molecular Target Assessment have been established. These Centers support interactive research and provide resources, flexible exploratory funds, and training and career development. NCI will also create new Centers of Excellence in collaboration with the NIH Center for Complementary and Alternative Medicine.

- The **Specialized Programs of Research Excellence** (SPOREs), the first Centers of Excellence, focus on specific cancers. Our 18 SPOREs serve as translational research engines that move discoveries back and forth among laboratory, clinic, and population research settings. The success of breast, prostate, lung, and gastroentestinal cancer

SPOREs has prompted an expansion of the program to other cancer sites, including four new SPOREs in ovarian cancer in 2000 and plans to launch SPOREs in skin, brain, and head and neck cancers over the next five years. The SPORE Program has evolved from an experiment with a few cancer sites to an established program targeted to include all cancer sites and types.

- To identify and evaluate biomarkers and technologies for earlier detection and risk assessment, NCI established the **Early Detection Research Network** (EDRN). The EDRN is a national network of academic and industry investigators, with expertise in laboratory and clinical sciences, biostatistics, informatics, and public health issues. Research funded through EDRN's 18 Biomarkers Developmental Laboratories, three Biomarkers Validation Laboratories, eight Clinical/Epidemiology Centers, and Data Management and Coordinating Center is already yielding results. EDRN-funded researchers have discovered a novel approach for detecting cancer based on mutations found in DNA in a cell's mitochondria. (See p. x.)

- NCI recently published the **Atlas of Cancer Mortality in the United States, 1950-1994**, showing geographic patterns of cancer death rates in over 3000 counties across the country. The 254 color-coded maps, which are accessible on the web (http://www.nci.nih.gov/atlas) make it easy for researchers and state health departments to identify places where high or low rates of cancer occur, and to uncover patterns of cancer that would escape notice if larger areas, such as states were mapped.

- The traditional classification of cancers is based on tumor structure, but structure alone does not always accurately predict a tumor's biological behavior, treatment response, or prognosis. NCI is seeking a more clinically predictive and useful classification system through our **Director's Challenge: Toward a Molecular Classification of Tumors**. Investigators funded by this initiative are creating comprehensive molecular profiles of tumors using DNA, RNA, or protein-based technologies. These profiles will identify clinically important tumor subsets and will provide more informative molecular classification schemes for human cancers.

- NCI has launched the **Diagnostic Imaging Network**, in partnership with the American College of Radiology, to support the testing of new and refined diagnostic imaging methods for cancer. The Network brings together imaging experts to perform a broad spectrum of multi-institutional clinical trials on imaging tools. A number of clinical trials have been launched or are in preparation, including a comparison of MR and CT in diagnosing gynecologic malignancies, the use of PET to follow response to chemotherapy, the value of spiral CT for detecting lung malignancies, a comparative study of digital versus conventional mammography, and a comparison of MRI versus CT for staging pediatric malignancies.

- To identify, characterize, and validate signatures, as well as apply this knowledge, we must continue to develop novel technologies and make molecular and analytic resources available. NCI is supporting peer-reviewed, high-risk, high-impact ideas that have the potential to revolutionize cancer research and cancer care through the **Unconventional**

Innovations Program (UIP). Five UIP contracts for "Novel Technologies for Noninvasive Detection, Diagnosis, and Treatment of Cancer" have been awarded. Complementary to the UIP is the **Innovative Molecular Analysis Technologies Program**, which has awarded over 80 grants focused on development and pilot applications of novel technologies for the molecular analysis of cancers and their host environment.

- To facilitate the development, testing, and adoption of new imaging modalities and applications, NCI has organized a unique **imaging forum** that brings together technology developers from academia and industry with the funding agencies, regulators, and reimbursers of technology. NCI's partners include the Food and Drug Administration, the Health Care Financing Administration, major device manufacturers through the National Electrical Manufacturers' Association, and other third-party payers and providers. These partnerships promote communication and progress in this critical area. The first meeting of the forum was held in September of 1999 and the second is planned for September of 2000.

The National Cancer Institute's Role in Cancer Research

The National Cancer Institute (NCI) is charged to lead our Nation's research effort to conquer cancer in all its forms. As the Federal focal point for cancer research in this country, NCI provides vision and leadership for the cancer research community. Each day, across the United States and around the world, thousands of NCI-funded researchers and clinicians are joined together by a common goal. They are all working toward the day when cancers are an uncommon and easily treatable set of diseases. NCI works to:

- Sustain at full measure our proven, productive research programs.
- Seize the extraordinary scientific opportunities made possible by our previous discoveries.
- Build our capacity for the future and address issues of special concern to the cause of cancer.

We also work to plan and implement national agendas for disease-specific research as part of our ongoing process of building upon broadly applicable research areas and capabilities to address the specific research needs of the more than 100 specific types of cancer.

Sustaining proven, productive research programs

NCI conducts, coordinates, and funds research across a vast continuum that includes cancer risk assessment, prevention, detection, diagnosis, treatment, survivorship, and end of life care. In support of the entire community of cancer researchers, NCI has developed an infrastructure of mechanisms, organizations, and networks that link scientists, facilities, and information. In addition to laboratory, population, translational, and clinical research, NCI supports investment in new research programs to address behavioral, surveillance, and communications research, as well as studies on the needs of cancer patients and survivors. We also support Cancer Centers, community-based clinical oncology programs, training opportunities, and communications, education, and outreach programs for both health professionals and the public.

Seizing extraordinary scientific opportunities

NCI systematically identifies areas in which focused efforts and increased resources could help reduce the burden of cancer. Through this effort, we select "extraordinary opportunities for investment" that promise to provide profound insights into how cancer develops and lead to major improvements in our ability to prevent, control, detect, diagnose, and treat cancer. The six Extraordinary Opportunities outlined in this document are in the final year of a three-year planning cycle. Identifying, planning for, and implementing extraordinary opportunities all involve extensive participation by our researcher and advocacy communities.

Building capacity for the future

As we learn more each day about the basic nature of cancer, we are faced with the challenge of converting these findings into improvements in cancer prevention and care. However, our ability to translate new knowledge and technologies into benefits for people has not kept pace with our discoveries. Therefore, NCI has identified eight areas in which intensified efforts are needed to open the current bottleneck restricting the most rapid application of discoveries to better cancer care. Meeting these challenges means ensuring that sufficient technological resources, trained scientists, and expanded infrastructures exist, and that the vision, creative environments, and diverse resources needed are available. Meeting these challenges also requires that we develop new knowledge and strategies to define, measure, and monitor the quality of cancer care and eliminate disparities in both cancer care and cancer outcome that now exist within our population.

National agendas for disease-specific research

NCI supports vital research programs that seek to answer the many remaining questions about how best to prevent and treat cancer. As we develop an understanding of biological processes common to several or even all tumor types, we gain new knowledge that can be applied to research on specific cancers. As we make discoveries about specific cancers, we are prompted to ask new questions about themes common to all cancers.

Broadly Applicable Research

Much of our research seeks to generate essential knowledge that can be applied to many types of cancer. This basic research uncovers features that are common to all normal, precancerous, and cancerous cells and aids in identifying molecular characteristics that distinguish one cancer from another. Distinguishing cancers according to their molecular characteristics is becoming as important as the traditional way of defining a cancer by the site in which it arises. Through basic research we have learned that one or more cellular mechanisms – cell growth, cell death, invasion, metastasis, avoidance of immune system attacks, and the accumulation of genetic changes that lead to cancer – are, in different combinations, responsible for most cancers. For example, by studying the pathways and genes that are mutated as a normal cell is transformed into a cancerous cell, scientists believe they have identified three key genetic changes that must occur in order for a cancer cell to develop. With this knowledge, researchers are now able to create cancer cells in the laboratory. The discovery of these essential steps in cancer progression might not have occurred without broad research into the basic biological processes common to all cancers.

Disease-Specific Research

Disease-specific research is aimed at uncovering biological characteristics that are unique to site-specific cancers such as breast or prostate cancer. Here the goals are to design effective methods of preventing, detecting, diagnosing, and treating the cancer, and to address disease-specific survivorship issues. For example, study of the very rare childhood cancer of the eye,

retinoblastoma, resulted in discovery of the *Rb* gene that, when altered, is the trigger that leads to retinoblastoma development. Scientists continued to study *Rb* and discovered the interconnected molecular machinery of a cellular circuit called the *Rb* pathway. This pathway is found in all cells, not just those that give rise to retinoblastoma, and at least one component of the *Rb* pathway is altered in every human cancer. Thus, a discovery unique to retinoblastoma eventually led to an understanding of a pathway that is found in all cells and has implications for all human cancers.

Four Types of Investigation

Our efforts to answer key cancer research questions through either broadly applicable or disease-specific research involve four types of investigation – laboratory, clinical, population, and translational. Laboratory research focuses on the biology of cancer, the fundamental properties of cancer-causing agents and processes, and the body's defense against and response to cancer. In the clinic, research is carried out on cancer prevention, diagnosis, treatment, and rehabilitation. Population research focuses on the causes, risks, predisposition, incidence, and behavioral aspects of cancer. Translational research builds bridges and intersections between and among laboratory, population, and clinical research. It facilitates the movement of discoveries from laboratory and population research into the clinic and, conversely, provides a way for clinical insights to inform laboratory and population-based research.

How We Carry Out Our Role

To carry out our role as the Federal focal point for cancer research, NCI conducts, coordinates, and funds cancer research and provides vision and leadership for the cancer research community. This requires us to:

- Plan and prioritize all aspects of our research.
- Conduct ongoing assessment to identify what is working well and what needs to be added or changed.
- Seek advice regularly from our diverse stakeholders through our various boards, committees, and community members.
- Carry out all of the activities required to support the cancer research enterprise.

Planning and Priority Setting

Research planning is an integral part of all NCI activities. Planning involves identifying needs and opportunities, setting priorities, developing strategies for implementing decisions and recommendations, and making sure that a reliable infrastructure supports all of our initiatives. Setting NCI's funding priorities is a complex and dynamic process designed to ensure that we:

- Support the full range of research activities necessary to conquer cancer through a balanced portfolio of research in behavior, epidemiology, control, prevention, detection, diagnosis, and treatment as well as survivorship, rehabilitation, and end of life issues.
- Give attention to the spectrum of distinct diseases we collectively refer to as cancer and the various populations that experience these diseases differently.
- Link all components of the cancer research enterprise through translational research.
- Look to our diverse constituencies to help us identify new opportunities, gaps, and barriers to progress; create new programs; and improve existing ones.

Assessment and Implementation

The cycle of planning and priority setting is completed through assessment of our programs and the breadth of the science we support. These assessment efforts, such as program reviews and progress reviews, often produce recommendations for changes to ensure that our research support structure is strong and our portfolio complete.

Program Reviews

NCI supports research through a variety of mechanisms, many of which provide funds tailored to specific research processes. To provide for ongoing review and revitalization, NCI has instituted a series of external reviews to guide us in strengthening our major research support programs. In the past few years, we have completed in-depth reviews of several programs: Cancer Centers, Cancer Control, Clinical Trials, Cancer Prevention, Developmental Therapeutics in Cancer, and Developmental Therapeutics in AIDS.

Progress Reviews

To assess NCI's research portfolios on specific forms of cancer, we seek the advice of experts through Progress Review Groups (PRGs). PRGs are composed of prominent members of the scientific, medical, and advocacy communities who are intimately familiar with the state of the science and can provide thoughtful, considered evaluation of our existing research, identify areas of need, and recommend activities that will speed our progress. (See "Planning National Agendas in Disease-Specific Research" on page X.)

Implementing Recommendations

Program reviews, progress reviews, and other assessment and advisory activities conducted at NCI generate both insights and recommendations on how best to organize a program or pursue a field of research. Implementing these recommendations is key to successful planning, as planning alone does not bring about change. To implement changes, we have formed groups of outside scientists and NCI staff that grapple with the redesign of programs and development of new initiatives recommended by the Program Review Groups, Progress Review Groups, and Extraordinary Opportunity Working Groups. Ongoing Implementation Groups include those focused on Clinical Trials, Prevention, Surveillance, Diagnostics, Tobacco Research, and Early Detection.

Advisory Activities

Seeking and incorporating expert advice is an essential element of NCI's cycle of planning, priority setting, assessment, and implementation. To ensure the wise use of resources to meet the goals of the National Cancer Program, NCI actively seeks out the expert advice of a variety of advisory bodies both within and outside the Institute.

National Cancer Advisory Board

NCI's principal advisory body is the Presidentially appointed National Cancer Advisory Board (NCAB). The NCAB, with a membership including scientific experts and advocates, advises NCI's Director on issues related to all aspects of the National Cancer Program and provides a second level of review for grant applications referred to NCI.

Board of Scientific Counselors

The Board of Scientific Counselors (BSC) advises the Institute leadership on the progress and future direction of NCI's Intramural Research Program. These scientific experts from outside NCI, along with consumer advocacy community representatives, evaluate the performance and productivity of NCI staff scientists through periodic site visits to intramural laboratories and advise on the course of each Division's programs.

Board of Scientific Advisors

With the BSC, the Board of Scientific Advisors (BSA) represents the scientific community's voice in the science NCI conducts and supports. The BSA, composed of distinguished scientists from outside NCI and representatives from the consumer advocacy community, advises the NCI leadership on the progress and future direction of the Institute's Extramural Research Program. The BSA evaluates Institute-awarded grants, cooperative agreements, and contracts and reviews ideas for new research solicitations to ensure that the concepts are meritorious and consistent with the Institute's goals.

Advisory Committee to the Director

The Advisory Committee to the Director advises and makes recommendations to the Director for the oversight and integration of various planning and advisory groups serving NCI's broad programmatic and institutional objectives, such as Director's Working Groups, Progress Review Groups, and the Special Populations Working Group. The Committee serves as the official channel through which the findings and recommendations emerging from these groups are submitted to NCI.

NCI Executive Committee

The NCI Executive Committee, which includes NCI Division directors and other key advisors to the Director, meets regularly to make major policy and operating decisions for the Institute.

Director's Consumer Liaison Group

Established in 1997, this first all-consumer advocate advisory committee for NCI consists of 15 members who represent the diverse face of consumer advocacy across the U.S. Its purposes are to:

- Serve as a primary forum for discussing issues and concerns and exchanging viewpoints important to the broad development of NCI program and research priorities.
- Help develop and establish processes, mechanisms, and criteria for identifying appropriate consumer advocates to serve on NCI program and policy committees.
- Establish and maintain strong collaborations between NCI and the advocacy community.

Community Input

Input from the community is very important to NCI. So that we can better understand the needs of cancer patients, those at risk for cancer, and interested parties in the lay community, NCI established the Office of Liaison Activities (OLA). As NCI's public liaison office, OLA fosters and enhances communication with this community and addresses the concerns of Congress and the community about how NCI sets research priorities. OLA maintains ongoing communications and information exchange between the national cancer advocacy organizations and NCI, encourages input and feedback from these organizations, and cooperates and collaborates with

these groups in areas of mutual interest. The Office supports the Division of Extramural Activities in expanding representation of consumer advocates on NCI peer review panels and coordinates and supports the Director's Consumer Liaison Group. OLA also builds relationships with professional societies and other Federal agencies, and provides input and perspective to NCI on complex issues relevant to cancer patients and the public.

NCI's Core Research Programs and Infrastructure

The national cancer research program represents our Nation's commitment to progress against cancer through science. Science cannot thrive – indeed, it cannot even take place – without the resources that support an enterprise of discovery. The engine that drives progress is the creativity, commitment, and hard work of researchers and clinicians whose discoveries and ideas are tested to find ways to understand, prevent, detect, diagnose, and treat cancer and to care for the people who have cancer, have survived it, or are at risk.

NCI's budget supports an extensive community of cancer researchers and an infrastructure of support mechanisms, organizations, and networks that link scientists, facilities, and information.

- About 73% of our budget supports basic and clinical studies conducted by researchers and clinicians across the Nation through our Extramural Research Program.
- We spend about 16% of our budget on our Intramural Research Program, in which NCI's own scientists conduct cancer-related research.
- About 4% of our budget is devoted to training, education, and career development of researchers and clinicians at every stage of their careers.
- We use about 3% of our budget to communicate the latest information about cancer risk, detection, prevention, treatment, rehabilitation, and control to people with cancer, health professionals, and the general public.
- About 4% of our budget supports the administration and management of the Institute.

Extramural Research

NCI's Extramural Research Program serves as our link to the greater scientific community and includes the Divisions of Cancer Biology, Cancer Treatment and Diagnosis, Cancer Prevention, and Cancer Control and Population Sciences. An essential component of the Extramural Research Program is NCI program staff. Their scientific expertise in cancer-related fields and national focus in a given research area enables them to work effectively with NCI-funded scientists in academia and industry to facilitate research progress and serve as a resource for researchers. Program staff:

- Synthesize the state of the science in important areas.
- Identify priorities for new research directions.
- Foster collaborations among scientists.
- Keep abreast of the research program through active communication with investigators.
- Organize scientific meetings to promote the interchange of information among investigators.
- Educate researchers on NCI policies, procedures, and grant preparation.
- Secure supplemental funds as deemed meritorious.

Finally, program staff monitor the progress of extramural grants through contact with individual investigators and annual research progress reports. Results of these NCI-funded projects are communicated to the scientific community and the public through peer-reviewed scientific journals, major scientific meetings, workshops, and symposia, and through our other cancer communication outlets, such as the Cancer Information Service, the Physician Data Query database, our press office, and our Web site.

Grant Mechanisms

The main pool of funds expended by NCI for awards to extramural scientists is known as the Research Project Grant (RPG) pool. These funds foster the creativity of talented scientists by providing them with the freedom to pursue the best ideas that will yield progress against cancer.

NCI funds two main types of research project grants: Single Research Project Grants awarded to institutions on behalf of individual principal investigators and Program Project Grants funded to foster collaborations among groups of scientists involved in related research projects. In Fiscal Year 2000, NCI anticipates expending more than $1.4 billion in support of over 4,300 separate research grants. More than 1,150 of these awards will be new or competing renewal projects. The single investigator grant payline rose from the 15th percentile in Fiscal Year 1995 to the 24th percentile in Fiscal Year 1999. These grant awards and the dedicated researchers behind them constitute the largest single categorical investment of resources that NCI, through the extramural research community, makes annually to combat cancer. Collectively, the Single Research Project and Program Project Grants span the full range of basic, clinical, population-based, and translational studies of cancer etiology, biology, prevention, detection, diagnosis, treatment, control, and survivorship. The advances that come from these investments, such as the discovery and development of important new anti-cancer drugs, and advances in the understanding of basic bone marrow transplant biology and its clinical application, represent the future of cancer research and cancer care.

NCI also has special mechanisms to fund exceptionally high-risk, innovative, exploratory, and developmental research activities, to allow investigators to embark on projects of unusual scientific potential, and to support research and development ideas that are likely to result in the development of a commercial product or service.

Intramural Research

NCI's Intramural Research Program (IRP), which consists of more than 400 principal investigators in the Divisions of Basic Sciences, Cancer Epidemiology and Genetics, and Clinical Sciences, is dedicated to the comprehensive understanding of cancer and to finding cures for these diseases. Organized to complement ongoing research in universities and in industry, the IRP has been involved in pivotal discoveries in cancer research: the first successful treatments for childhood leukemias; establishing the principles for curative chemotherapy for lymphomas; developing effective therapies for HIV; defining the foundations for tumor vaccines; identifying genetic causes of familial cancers; and uncovering environmental causes of cancer.

The IRP's epidemiology research program is a national program of population-based studies to identify environmental and genetic determinants of cancer. This IRP component supports epidemiologic and interdisciplinary research to ensure that the momentum of recent and ongoing discoveries in molecular genetics and cancer biology is accelerated and broadened through population-based studies into the etiology of cancer and its prevention.

The intramural clinical research program is conducted principally in NIH's Warren G. Magnuson Clinical Center. It provides the opportunity for patients from across the country to be treated through groundbreaking research protocols. The Clinical Center is a unique environment in which investigators throughout the NIH community develop and test novel therapies derived from our growing body of knowledge. In this environment, new information can be transferred quickly from the laboratory to the patient and back to the laboratory for additional analysis.

The IRP is uniquely structured to address cancer research problems whose resolution requires long-term commitments and that may be considered unsuitable for many extramural funding mechanisms. Another unique aspect of the IRP is its framework for cooperation between basic researchers and investigators performing clinical trials. These interactions, fostered by common research interests, topic-specific focus groups and retreats, and the close physical proximity of basic and clinical research efforts, result in rapid translation of new basic research discoveries into early clinical trials.

As we move into the new century, our goal is the same, to move concepts between the scientific disciplines in order to find cures for cancer. However, we will change our approach to meet new scientific challenges. We will augment our work in validating new technologies in clinical cancer research, that assess the molecular fingerprints of cancer, that allow for imaging of biochemical functions, and that can test the presence of miniscule amounts of cancer associated proteins. We will move towards integrating clinical and basic sciences in identifying and testing new molecular targets for cancer therapies. Lastly, we will explore new information technologies that will allow us to better analyze the large amounts of data currently being generated. We will also define new electronic media that will assist in medical communication at remote sites.

Because of its national stature and unique structure, NCI's IRP is also a center for basic, clinical, and population-based oncology training for researchers, clinicians, research fellows, and visiting scholars from around the world. NCI plays a major role in fostering the education and careers of a growing number of nurses, doctors, and physician assistants, as evidenced by the approximately 500 participants each year in the summer intramural research training program. Many of the current leaders in cancer research received some of their training at NCI, and we anticipate that the IRP will continue to be an important resource for training the next generation of investigators.

Clinical Research

Clinical research is one of the cornerstones of the National Cancer Program. Every new treatment we use today, every preventive measure that is widely recommended, and every innovative detection strategy has been, at one time, tested in cancer patients or in people at risk

for the disease. These heroes of the fight against cancer have allowed us to amass the body of information we are building upon every day. Clinical trials test the new therapies but provide no guarantees of success. A participant may be randomly assigned to a control group to receive standard therapy or may participate in a Phase I or II trial too early in a drug's development to be sure of its effectiveness. Nonetheless, trials provide participants access to cutting-edge interventions and provide researchers with information that ultimately will enable us to prevent and effectively treat all cancers.

Strong intramural (see previous section) and extramural clinical research infrastructures, including a comprehensive program of clinical trials in treatment, early detection, and prevention, are vital components of NCI's research program. NCI's Cancer Centers, Cooperative Groups, and Community Clinical Oncology Program comprise our extramural clinical research program where findings from the laboratory are translated into new treatments, diagnostic tools, and preventive interventions, and where these measures are first tested for safety and effectiveness. These programs are fundamentally interrelated. Every Cancer Center is a participant in at least one Cooperative Group and Cooperative Groups serve as research bases for participants in the Community Clinical Oncology Program. Hundreds of clinical trials are supported through these and other research mechanisms such as Single Research Project Grants, Program Project Grants, cooperative agreements, and contracts.

NCI's programs in clinical research have enjoyed many notable successes over the years. NCI has been responsible for the early development and/or testing of many important treatments, including paclitaxel (Taxol®) for breast and ovarian cancer, interferon alpha-2b for malignant melanoma, and Herceptin® for breast cancer. Studies to test the effectiveness of certain drugs to prevent first occurrences of cancer include the ongoing Prostate Cancer Prevention Trial. Results of the Breast Cancer Prevention Trial led to Food and Drug Administration approval of the drug tamoxifen (Nolvadex®) to reduce the chance that women at high risk of breast cancer will develop the disease. NCI has already launched the Study of Tamoxifen and Raloxifene (STAR) to compare tamoxifen to raloxifene, a promising breast cancer prevention agent that may have fewer side effects than tamoxifen.

Through our clinical research programs, we have also identified successful interventions for symptom management and continuing care of cancer patients, including treatment for mouth sores and hot flashes, both common side effects of chemotherapy. And based on the results of laboratory research, we are now exploring interventions for individuals whose genetic profile places them at increased risk of cancer.

Of primary concern at this juncture is that our ability to conduct clinical trials is in danger of being compromised by changes in the health care system. In the past, institutions have used surplus revenues from patient care services to supplement government research support. The growth of managed care has all but eliminated those discretionary funds. As a result, institutions can no longer sponsor research activities requiring capital expenditures and cannot support essential training for young investigators. Because no mechanism is in place to replace these funds, these changes pose a very real danger for the continuation of cancer research and our continued progress against cancer.

In response to the changing health care system, NCI has been developing ways to improve access to and participation in clinical trials. To ensure that physicians have the time to conduct clinical trials, we have developed a Mid-Career Investigator Award in Patient-Oriented Research that offers subsidies to clinicians, allowing them protected time to devote to vital patient-oriented research (See our Training Challenge, p. x.) Further, through agreements with private insurers and other government agencies, we are working to assure insurance coverage for individuals participating in trials. We have two government interagency agreements, one with the Department of Defense (DoD) that provides coverage for DoD health plan beneficiaries to participate in NCI-sponsored cancer treatment and prevention trials, and a second with the Veteran's Administration that covers the full range of NCI-sponsored clinical trials. In addition, an executive memorandum recently issued by the President directs the Medicare program to reimburse providers for the cost of routine patient care in clinical trials, and it provides for additional actions to promote the participation of Medicare beneficiaries in clinical studies.

Based on these models, several organizations have enacted agreements at the local, state, and national levels to provide greater access and coverage for clinical trials. For example, the United Health Care Corporation has agreed to provide coverage of patient care costs associated with cancer treatment trials conducted by the NCI-supported Coalition of Cooperative Groups. Several states have also enacted legislation designed to provide greater access and coverage for clinical trials. In addition, NCI is working with patient advocates, local communities, and non-profit organizations to increase awareness of and education about clinical trials.

Cooperative Group Clinical Trials Program

The sheer number of different types of cancer and their biological complexity make the process of efficiently identifying and evaluating new treatments or other anti-cancer strategies extremely challenging. To test potential treatment advances more rapidly, NCI maintains the Cooperative Group program. This national network consists of 12 consortia (Cooperative Groups) that seek to define the key unanswered questions in cancer and then conduct clinical trials to answer them. Each year, 1,700 institutions throughout the United States and Canada, and approximately 8,000 investigators in these institutions participate in these trials. This kind of cooperation makes it possible to centralize administration and data collection for trials taking place at a large number of sites around the world. The Cooperative Groups differ in structure and research organization, but they share the common purpose of developing and conducting large-scale trials in multi-institutional settings.

Cooperative Groups frequently work together when the cancer in question is so rare that one group working alone would be unable to accrue enough patients to conduct a meaningful study. For example, six Cooperative Groups worked together on the landmark study establishing that all-*trans* retinoic acid (ATRA) significantly improves disease-free survival time for patients with acute promyelocytic leukemia. Cooperative Groups collaborate regularly on clinical trials for solid tumors in children, breast cancer, colorectal cancer, lung cancer, prostate cancer, and cancers of the head and neck.

Approximately 20,000 patients participate in Cooperative Group clinical trials each year, principally in large Phase III trials that help establish the state of the art for cancer therapy. Many new anti-cancer drugs are tested in patients for the first time under NCI Investigational New

Drug (IND) sponsorships through the Cooperative Group program. Approximately 200 investigational agents or treatment strategies, ranging from new chemotherapy drugs and cancer vaccines to agents that prevent tumor blood vessel development, are currently being studied under NCI INDs.

An agreement between the U.S. Office for Protection from Research Risks and the European Organization for Research and Treatment of Cancer (EORTC) will improve the ability of NCI's Cooperative Groups to collaborate with the EORTC and other international cancer research groups.

Community Clinical Oncology Program

The Community Clinical Oncology Program (CCOP) is a network of 49 central offices in 31 states that provides the infrastructure to link more than 2,500 community cancer specialists and primary care physicians with clinical Cooperative Groups and Cancer Centers. In addition, CCOPs support scientific development and the implementation of ongoing cancer treatment, prevention, and control clinical trials among community Cooperative Group members and Cancer Centers.

This network enables individuals to participate in state-of-the-art clinical research trials at over 340 community hospitals without the burden of traveling to a distant site. Each year, the program enrolls more than 5,000 patients in cancer treatment clinical trials and additional 3,500 patients in cancer prevention and control clinical trials. An additional seven Minority-based CCOPs increase the participation of minority individuals in clinical trials research. Each year, over 700 patients enter clinical trials through these specialized CCOPs. Located in six states and Puerto Rico, these programs bring additional 33 hospitals and 250 physicians into the clinical trials network. By increasing the number of patients and physicians who participate in clinical trials, the program helps transfer the latest research findings to the community.

Cancer Centers

Fifty-nine research-oriented institutions throughout the Nation have been designated NCI-supported Cancer Centers in recognition of their scientific excellence. The Centers are key partners in NCI's efforts to speed the process of discovery and bring the benefits of cancer research directly to the public. Located throughout the country, Cancer Centers are hubs of cutting-edge research, high quality cancer care, and outreach and education for both health care professionals and the public.

When an institution meets the rigorous competitive standards to become an NCI Cancer Center, it is awarded a Cancer Center Support Grant. These funds enable the institution to coordinate multidisciplinary approaches to research questions, to gain access to the most advanced research technologies, and to take rapid advantage of new research opportunities. Support for the Cancer Centers helps ensure a close association between state-of-the-art research and state-of-the-art care activities within the institution. Moreover, it allows each Center to develop key collaborations with industrial, community, and state health organizations, and to link the research capabilities and expertise of scientists within the institution to problems of cancer incidence and mortality in their communities and regions.

Three types of centers exist: Cancer Centers have specific research foci, such as epidemiologic or basic research; Clinical Cancer Centers integrate basic science with clinical science; and Comprehensive Cancer Centers demonstrate both significant scientific strength in basic, clinical, and population studies and strong interdisciplinary collaboration. Comprehensive Cancer Centers also must have in place effective cancer information, education, and outreach activities for the regions and communities they serve.

Traditionally, Cancer Centers have had broad scientific bases, and most have been developed within a single institution. Changes in the program, however, are enabling the planning of new consortia of institutions, often linking free-standing clinical and academic centers with community hospitals to form networks with tremendous research strength and the ability to deliver quality care in a managed care environment. In addition, more focused scientific concepts are being developed for Cancer Centers. For example, some Centers are focusing on population sciences and others are concentrating on translational research opportunities within a specific scientific discipline, such as immunology. Overall, such changes in the Cancer Centers program promise to increase the scientific versatility, translational research capabilities, and geographic distribution of NCI-supported Cancer Centers.

Cancer Control

Cancer control research encompasses basic and applied research in the behavioral, social, and population sciences aimed at creating or enhancing interventions that, by themselves or in combination with biomedical approaches, reduce cancer risk, incidence, morbidity, and mortality, and improve quality of life. For example, a cancer control study might investigate the use of a medical intervention, such as a nicotine patch, in combination with a behavioral intervention, such as a counseling program to help smokers overcome their barriers to quitting. Interventions may be directed at patients, physicians, and/or other health care providers. Cancer control research seeks to improve interventions across the human lifespan and over the entire cancer continuum, and to move research findings into clinical and public health practice. The foundation of cancer control research is epidemiology. Surveillance and outcomes research are the fundamental mechanisms for assessing progress.

NCI maintains a firm commitment to cancer control research through the Division of Cancer Control and Population Sciences (DCCPS), the focus for NCI-sponsored research programs aimed at studies of populations, behavior, surveillance, special populations, outcomes, and other aspects of cancer control. Our wide-ranging cancer control research efforts include research in epidemiology and genetics, tobacco research, tailored communications, and theoretical models for studies of human behavior and behavior change.

Cancer surveillance – tracking and analyzing trends in cancer incidence, mortality, and survival rates – is a critical component of cancer control. The keystone of NCI's surveillance efforts is the Surveillance, Epidemiology, and End Results (SEER) program. The SEER program monitors the Nation's cancer burden and provides the basis for assessing individual, organizational, and societal factors that can reduce cancer rates. (See page xx for further information on cancer trends.)

AIDS Research

Malignancies occur in more than 30 percent of AIDS cases and contribute greatly to AIDS morbidity and mortality. Many areas of fundamental biology developed in NCI programs, including virology, immunology, and cellular and molecular biology, are directly applicable to understanding HIV and AIDS. Research efforts in AIDS malignancies begin with basic science that provides new insights in cancer biology that can lead to hypotheses to test in epidemiologic studies, the development of treatment targets, and new treatments to prevent and control AIDS malignancies. But basic science, even with associated drug development programs, would not make progress without clinical programs in which to test potential discoveries. Work in this area is necessarily collaborative and one of NCI's major roles is to foster these collaborations, create research groups, and provide infrastructure, including clinical trials support, central specimen banking, international scientific meetings, and new investigator training.

Research into the fundamental biology of HIV and AIDS, AIDS treatment, and particularly AIDS-related malignancies takes place throughout all programmatic mechanisms of NCI. The Intramural Research Program is an internationally recognized center for research in HIV and AIDS, housing the HIV Drug Resistance Program, the HIV and Malignancies Branch, and the NIH Vaccine Research Center, a joint project with the National Institute of Allergy and Infectious Diseases. The Extramural Research Program also has been a vital and innovative force in this area of research. Among its programs are the AIDS Malignancy Consortium, the AIDS Malignancy Bank, the AIDS Oncology Clinical Scientist Training Program, and an annual international forum on AIDS malignancies. NCI, in coordination with other NIH Institutes and the NIH Office of AIDS Research, continues its commitment to meeting the challenge of AIDS and is working to ensure that NCI-supported AIDS and AIDS-related research is integrated with national AIDS strategies.

Training and Education

In the past decade, we have made stunning advances in our understanding of cancer. Our ability to bring these new discoveries to the communities and clinics where they benefit cancer patients and those at risk for developing cancer depends on physicians and other scientists who are specially trained in cancer research. While resources for training are shrinking at many institutions, NCI is committed to ensuring that a national cadre of trained cancer researchers exists by continuing to provide essential training to our Nation's scientific and medical workforce.

To address this crucial requirement, NCI is implementing a long-range plan for extramural training, education, and career development. This plan focuses on attracting young scientists into cancer research, on providing stability and protected research time for researchers in disciplines critical to translational research, on creating more opportunities for underserved ethnic and minority scientists, and on encouraging research program diversification. In pursuit of these objectives, NCI has implemented a number of new training and career development programs in basic, clinical, population, and diversified sciences, as well as for underserved ethnic and minority groups who are underrepresented in the research workforce. These programs aid

investigators in stabilizing and sustaining productive research careers, and offer opportunities for engaging in translational research (see the Training Challenge, p. X).

NCI also sponsors a number of training programs related to specific fields of study. For example, the Division of Clinical Sciences' Clinical Intramural Research Award supports innovative and collaborative clinical research projects emphasizing novel approaches or promising new outcomes of current research. The Division of Cancer Epidemiology and Genetics' Fellowship Program provides interdisciplinary training in clinical, molecular, and quantitative genetics, and genetic epidemiology. And, the Division of Cancer Prevention Fellowship provides training in cancer prevention and control for individuals from many health science disciplines.

Other Research Support

In addition to its many types of grants and awards, NCI employs a variety of other research support mechanisms. These mechanisms include:

- Contracts to provide support for research, information dissemination, and management
- Conference grants to fund meetings, conferences, and workshops
- Resource-related research projects to improve the ability of resources to serve biomedical research
- Scientific evaluation awards to support the scientific review of grant and contract proposals
- Construction grants and contracts to provide partial support for modernizing or developing cancer research facilities throughout the Nation

NCI also sustains, guides, and monitors both the extramural and intramural activities of the Institute through its research management and support activities. These activities include overall scientific program direction and administration by the Office of the Director, with assistance from grant and contract science managers, finance, human resources, legislation, science program direction and assessment, and technology transfer staff. The review and oversight activities of the National Cancer Advisory Board and President's Cancer Panel are also included. This part of the budget also supports a share of central NIH facilities and operations, and extramural program staff salaries (intramural staff salaries and intramural facilities maintenance are included under the intramural research budget).

The NCI Organization (sidebar)

To be developed.

Understanding Clinical Trials (sidebar)

What are Clinical Trials?

Clinical trials are research studies conducted to answer specific scientific questions about new ways to prevent, diagnose, detect, and treat cancer. Most clinical trials are designed to test new cancer treatments. Concurrent or separate studies may be conducted to look at the psychological impact of cancer or ways to improve a patient's quality of life. In addition, the number of clinical trials to test drugs for cancer prevention has been increasing because of success with large precedent-setting prevention trials such as the Breast Cancer Prevention Trial.

Before a clinical trial of a promising new treatment or preventive agent can be launched, the agent must undergo rigorous laboratory testing to prove that it may be beneficial to patients and will be safe to use during testing. If the agent is promising and is safe for use, researchers then design a trial in an effort to answer a specific scientific question about the agent's use or efficacy. The researchers must establish strict entry criteria to help identify patients who are best suited for the trial. Only then can the researchers recruit volunteers to participate. Trials generally are conducted in three phases:

- **Phase I** — Small trials designed to tell researchers how best to administer a new intervention and, in studies of new agents, the optimal dose of the drug to give with the least possible side effects.
- **Phase II** —Studies involving small numbers of people to determine if the treatment, delivered at the optimum dose, destroys or prevents cancer and against what types of cancer it works best.
- **Phase III** — Trials to compare the efficacy of a new therapy that has been proven to have an anti-cancer effect and be safe with that of a standard therapy. Phase III trials are often large and may include hundreds or thousands of people from across the country.

As each phase of testing is completed, the data collected are analyzed and the results published. Based on this analysis, the researchers determine whether the agent is showing enough of a benefit to continue testing. Once a therapy has successfully completed these three phases of testing, a New Drug Application is submitted to the U.S. Food and Drug Administration. The testing and approval process can take many years, although the approval process can sometimes be accelerated, particularly if the agent is beneficial for patients with a form of cancer that has few treatment or prevention options. Occasionally, additional trials (called **Phase IV** trials) are conducted after initial drug approval to provide longer-term safety data or to collect new types of information, such as quality of life assessments.

Ensuring Diversity in Clinical Trials Participation

Ensuring participation in clinical research, particularly among women and members of special population groups, is a high priority for the Institute. Several programs help us ensure that all populations are well represented. The Minority-Based Community Clinical Oncology Program, begun in 1990, has been successful in accruing minority cancer patients to trials and provides for studies in minority populations that may lead to better understandings about the dynamics of patient accrual. In addition, two grant programs are supporting research on ways to draw more women and minority participants into prevention and screening studies. The Institute also has funded several

conferences aimed at sharing current information and strategies to maintain and enhance its good record of minority accrual to clinical trials.

As a result of our efforts, analysis of accrual patterns in Cooperative Group cancer treatment trials has shown that women and ethnic/racial minorities are proportionally represented in NCI cancer treatment trials. Nearly 20 percent of the more than 20,000 patients entering treatment clinical trials every year are members of an ethnic/racial minority group.

Informing Professionals and the Public – NCI's Information Services (sidebar)

Every day, thousands of people – health professionals, cancer patients and their families, and the general public – benefit from NCI's broad array of information and public education services. Using basic printed materials, sophisticated Internet technology, and everything in between, NCI provides millions of people each year, often in Spanish as well as English, with the complete, reliable information they need to make decisions about cancer prevention, detection, treatment, and follow-up care. NCI's services include:

- The **Cancer Information Service (CIS).** This nationwide cancer information and education network, available in all 50 states, Puerto Rico, and the U.S. Virgin Islands, receives more than 2,000 calls each day. By calling 1-800-4-CANCER (1-800-422-6237), cancer patients, their families, people at risk for cancer, and health professionals can receive information confidentially on all aspects of cancer including prevention, treatment, and clinical trials. Callers with TTY equipment can dial 1-800-332-8615.
- NCI's **Internet Services**. Patients and health professionals with access to the Internet may search for accurate, up-to-date information about cancer on **NCI's Web site** (http://cancer.gov). Our **CancerNet™** and **cancerTrials™** Web sites can be accessed directly from NCI's home page.
- **Physician Data Query (PDQ®)**. The CancerNet™ searchable PDQ® database contains current information on cancer prevention, screening, treatment, and supportive care as well as descriptions of active clinical trials and directories of physicians, health professionals who provide cancer genetics services, and organizations involved in cancer care.
- **CANCERLIT®**. This bibliographic database contains more than 1.4 million records on cancer literature from 1963 to the present. It can be searched from the CancerNet™ Web site.
- The **PDQ/CANCERLIT® Service Center**. Physicians and other health professionals can make requests for PDQ and CANCERLIT information through a toll-free telephone service, 1-800-345-3300. They also can send an e-mail to cancermail@icicc.nci.nih.gov with the word "help" in the body of the message to receive a contents list and ordering instructions by return e-mail. Or, they can make a request by sending a fax to 301-402-5874.
- **Print Publications**. NCI makes available nearly 600 publications and audiovisual materials, many published both in English and Spanish. They are available from the toll-free number 1-800-4-CANCER or from the NCI Web site. NCI also is developing materials in several Asian languages.

Planning National Agendas in Disease-Specific Research

When we read about cancer's toll on the American people, we are struck by the overwhelming number of individuals affected. *1.2 million new cases diagnosed in 2000. Half a million people dead this year. 8.4 million with a history of cancer right now.* Given these daunting statistics, we sometimes lose sight of the fact that the over 100 different forms of cancer are each a separate disease that affects people in different ways - each with its own distinct molecular, cellular, or tissue characteristics. What is important to the lives of patients, families, and friends is how to cure the cancer affecting them. The study of the unique features of each cancer is a crucial consideration as NCI plans for scientific discovery.

Five years ago, the NCI instituted a new comprehensive, dynamic planning process that incorporated three separate – but equally vital – elements. One element involves the intensive review of the large programs that support scientific discovery and application of discovery to human health – a process that currently forms the basis for the "Challenge" section of this document. A second involves investment in scientific areas that are broadly applicable to all cancers, as discussed in this document's "Extraordinary Opportunities" section. The third element of our process is disease-based planning.

The two research approaches – broadly applicable and disease-based – appear to be divergent, and indeed, a very real tension does exist between our exciting opportunities for broad scientific discovery and the urgent medical and public health needs of people with specific cancers. But they are inextricably linked. As we develop an understanding of biological processes common to many tumor types, we gain new knowledge that can be applied to cancer-specific research. And as we make discoveries about a specific type of cancer, new questions about themes common to all cancers are prompted.

When the NCI began its new approach to planning five years ago, we first identified the broadly applicable scientific opportunities through which vital progress could be made quickly. We then began a comprehensive review of the large programs that support discovery. Once these things were well underway, we stepped back and asked ourselves, "Can these broad investments be tailored to specific cancers? Have we developed the tools and infrastructure to conduct disease-specific research, and to do it well? Have we defined those broad-based research areas that can best support our disease-specific efforts?" Our efforts to answer these questions culminated in the creation of a new vehicle for planning disease-specific research: the Progress Review Groups.

PRGs: The People, the Process, the Plan

Progress Review Groups (PRGs) are panels of experts who are convened to develop a national research framework for individual types of cancer. The PRGs assess the state of the science, identify gaps in knowledge and barriers to progress, and identify research priorities. After

significant deliberation, each group produces a written report that represents a plan for making progress against the disease.

PRGs are composed of 20-30 prominent members of the scientific, medical, and advocacy communities who know the state of the science intimately and can provide a thoughtful, considered assessment of our portfolio and recommend activities that will speed our progress. Using the NCI's current research program as a baseline, each PRG outlines and prioritizes research areas for the particular cancer under study. Two Co-Chairs, widely recognized as leaders in their field, are named to lead the group's work, and an Executive Director from NCI is named to serve as the Institute liaison and to coordinate the PRG process.

Each PRG is given a compelling charge: *To imagine and build the future.* In imagining the future, the groups engage the scientific, medical, and advocacy communities in a dialogue regarding potential directions for research. PRGs also kindle the interest of the best scientific minds in research on specific cancers. And in spotlighting the gaps in our knowledge, and recommending how those gaps can be filled, the PRGs give the NCI the tools it needs to build the future.

The complete PRG process is intensive and extends over a number of months. [**Note: More on specific progress –e.g., Roundtable?]** To date, PRGs have been completed for breast, prostate, and colorectal cancers. A Brain Tumor PRG, conducted in collaboration with the National Institute of Neurological Disorders and Stroke, is nearing completion. Ongoing and planned PRGs are outlined in the chart on page xx.

Our Commitment: We Will Listen and We Will Act

The NCI is committed to responding rapidly and enthusiastically to the PRGs' recommendations. For each PRG, we:

- Undertake an analytical mapping exercise in which we determine to what extent the PRG's recommendations are being addressed – or could be addressed – by existing programs or efforts.
- Develop an implementation plan for the recommendations, and discuss that plan with the PRG.
- Communicate our decisions to the scientific community, and enlist their active participation in the implementation process.
- Ensure that effective mechanisms are in place to implement decisions.
- Follow up to ensure that the recommendations continue to be addressed.
- Report on our results.

Based on the PRGs' recommendations, NCI may modify existing programs or activities, or even create new ones. For example, the Breast Cancer PRG noted that our lack of understanding of the biology and developmental genetics of the normal breast was a significant barrier to progress against the disease. The NCI responded by releasing a Program Announcement, in conjunction with several other NIH Institutes, seeking applications for research on normal breast

development, as well as on changes in the breast throughout the development of early and advanced cancer.

The NCI responds to the PRGs in other ways as well. The PRG reports are considered broad Program Announcements notifying the scientific community that we are seeking applications for research projects focusing on a specific disease, and grant applications that reference a PRG report receive special consideration in the funding exceptions process (for more on the exceptions process, see page xxx). The NCI also publicizes the PRGs' findings widely, and publicizes on the Internet and in scientific journals all of its current opportunities related to the organ sites covered by the PRGs.

What We've Learned

With three PRGs completed, and more underway, the NCI has begun to take stock of its efforts to support disease-specific research. The results, to date, have been encouraging. Through our analytic mapping exercises, we've found that about 80 percent of the PRGs' recommendations map to programs that are already in place, or to programs that can be modified to address the recommendations. In fact, there are core scientific needs – for example, the need for research training, or for the development of biomarkers of disease – that appear to be universal, regardless of the disease. A certain percentage of recommendations represent genuine gaps in research or infrastructure that the NCI must and will address. A few recommendations fall outside the Institute's purview (e.g., Medicare reform [or other example]), and the NCI's response will necessarily involve advising other organizations or agencies, rather than acting directly.

These results indicate to us that we're on the right track. Equally gratifying has been the response of the community, which has been very receptive to the PRGs and their findings. But our short-term analysis does not go far enough. We must now determine whether this new paradigm for disease-based research planning makes a difference in research – and discovery – over the long term. To that end, we are now beginning to develop a process for evaluation of the PRG process and outcomes. This process will be in place by next year, and will provide valuable information and insight about our directions in disease-based planning.

"There's So Much More We Can Do": A Talk with a PRG Co-Chair

Harold Moses, M.D., is Director of the Vanderbilt Cancer Center in Nashville. In 1998, he served as Co-Chair of the NCI's Breast Cancer Progress Review Group. Recently, we talked to Dr. Moses about his experiences on the PRG, as well as his views on the future of breast cancer research.

Why do we need Progress Review Groups?

PRGs allow us to convene a group with diverse backgrounds to step back and take a look at where we are, and to speculate on where we should be going in cancer research for maximum

benefit. PRGs also serve to show Congress and the public that NCI really does have a reasonable planning process, and they indicate directions for future research.

This attracted me to the process when Dr. Klausner asked me to serve as co-chair. It looked like chairing the PRG would be fun, and it seemed that through the process, we might come out with broad recommendations for the funding of breast cancer research.

What is realistic to expect from the PRG process? What are its limitations?

It's realistic to expect PRGs to give a picture of where the research is now, and a broad outline of where it should be going. PRGs are also good for identifying areas of critical need.

In terms of limitations -- the PRGs can only give a "snapshot in time" of the state of the science, or of research needs, or of exciting opportunities. Things change. The danger would be if the NCI tried to adhere too rigorously to a plan made in the past. A PRG report is like any strategic plan – it's a "work in progress that needs to be modified continuously to address changing opportunities and needs.

Looking specifically at the Breast Cancer PRG, what do you consider to be the most valuable things to come out of the process?

Well, it's difficult to place a value judgment on this. But the realization of how little we know about the basic biology of the mammary gland, and about the progression of cancer from normal to pre-cancer through metastasis, was certainly very important. The group recognized how important an understanding of normal breast biology would be to designing clinical trials, as well as identifying surrogate endpoints and markers for studies of all kinds**,** including epidemiologic and prevention studies.

While the Breast Cancer PRG was going on, NCI had many other ongoing working groups, and they were making similar recommendations. It's amazing how similar the recommendations coming out of the breast group were to those coming out of the Prostate PRG, for example. So the recommendations we were coming up with were not necessarily unique, but they were critical to the advancement of science in a number of areas.

Are you satisfied with the NCI's response to the PRG's recommendations?

I was absolutely amazed at the NCI's response; it was fantastic, in my view. Some of the most exciting aspects of the NCI's response, to me, include the increased funding for investigator-initiated grants, especially those in basic biology and early progression; the renewed emphasis on mouse models; and the CGAP [Cancer Genome Anatomy Project] movement to incorporate some of our recommendations, such as the development of gene expression profiles for normal breast tissue in addition to breast cancer.

What did the Breast Cancer PRG reveal about the current state of breast cancer research?

It showed us that we've come a long way relative to five or ten years ago. We've made enormous advances, and that includes advances in basic science that are applicable to all types of cancer. It's now becoming clear in the survival rates that breast cancer can be more of a chronic disease, not a disease that is invariably fatal.

Another thing that came out of this group was the critical importance of basic research to progress in breast cancer, and the recognition of its importance to all the groups at the table – basic scientists, clinicians, epidemiologists, prevention researchers, and so on. PRG members in all of those disciplines recognized the urgent need for advances in basic research.

What would you like to see happen in the future in breast cancer research?

I would like to see us figure out better preventive measures against breast cancer, as well as treatments that will cure the disease with minimal side effects. A major need is to figure out how to do Phase II clinical trials more quickly and efficiently. There are so many amazing treatment agents in the pipeline – targeted agents with very low toxicity. Figuring out how to use those in the most appropriate way is a major challenge.

We also need better diagnostic criteria. We need to know which pathways are altered in precancer, early cancer, metastatic cancer. In addition, we need to keep plugging along in normal biology.

What I would foresee is that someday, we'll be able to get the gene expression profile for each individual cancer, then administer a treatment that's targeted to that cancer at the molecular level, likely in combination with a standard treatment. It's unlikely that any single treatment will be effective against all breast cancers.

There are a lot of opportunities right now in breast cancer research, but they involve a lot of work. It's exciting; there have been many important accomplishments – there's so much more we can do.

The Cancer Scientific Outline

The NCI's Cancer Scientific Outline (CSO) is a straightforward tool that was originally developed to allow categorization of NCI-supported research in a scientific and disease-related manner. It grew out of the NCI's experience with PRG and disease-specific Task Force efforts that were conducted in the past several years, and was developed by the NCI with significant input from the Department of Defense (DoD) Congressional Directed Medical Research Program.

Since the its inception, other cancer funders have expressed an enthusiastic interest in using the CSO to code and analyze their portfolios. The Department of Defense has committed to coding their complete portfolio to the outline, and several other state and non-profit organizations have been invited to participate in a pilot project to use the CSO to code their portfolio. The NCI is also instituting an Editorial Board, which will have representatives from each organization in the pilot, to address any needed changes to the CSO.

Ultimately, the entire NCI research portfolio will be available through a user-friendly CSO Web site tailored to audience needs. Using this Web site, users will be able to explore, browse, and analyze the portfolio. In addition, the NCI plans to work with other participating cancer research funders towards building an integrated Web site that would allow search capabilities across participating agencies and institutions.

Although simple in design, the CSO is likely to have a profound impact on shaping disease-related research and scientific planning by creating the critical foundation upon which informed discussions can be undertaken. The CSO will also foster coordination between NCI, DoD, and other cancer research funding organizations in order to eliminate duplication of funding and targeting research funding gaps.

Extraordinary Opportunities for Investment

Over the past 30 years, we have witnessed dramatic breakthroughs in our ability to understand and fight cancer. The revolution in molecular biology, along with the emergence of powerful new technologies, has enabled us to gather an impressive body of knowledge about the nature of cancer. As a result, we are now able to identify many of the biochemical pathways in a cell that become disrupted in cancer, and we are gaining a fuller understanding of how such changes contribute to the abnormal and dangerous behavior of a cancer cell in the body. We are gaining important insights into how the vulnerability our genetic material, elements in our environment, and the lifestyle choices we make may interact to give rise to cancer. Many who struggle with cancer are experiencing marked improvements in treatments and a heightened chance for survival as a result of these striking changes in the science and technology of cancer research. As a result of these discoveries, scientists have also been able to develop more effective prevention measures, particularly for people who may be at increased risk.

These advances have allowed us to make significant progress, but our work is not complete as long as people continue to suffer from cancer. To conquer cancer, we must choose a path that not only maintains our pace of discovery but speeds progress by optimizing every opportunity for scientific advancement. This path requires science that is anchored in exceptional quality, marked by vision, imbued with imagination, and tenaciously follows opportunities for discovery.

As a key component of our ongoing planning process, NCI identifies areas of "extraordinary opportunity for investment." These are areas of cancer research in which focused efforts and increased resources would build on past successes to produce dramatic progress toward reducing the burden of cancer. If pursued, these new doors to continued discovery promise to provide profound insights into how cancer develops and lead to vastly improved techniques to prevent, detect, diagnose, and treat the various forms of cancer.

The process of identifying these areas of exceptional promise in the cancer field began in 1996 with formal input from over 60 cancer scientists, educators, advocates, and community leaders. In 1998, as a first three-year cycle drew to a close, NCI again approached scientific, professional, and lay experts in the cancer field to revisit the "extraordinary opportunities" and select emerging investment research areas for the next three-year cycle. NCI received more than 250 responses from our grantees, members of our advisory boards, and advocacy groups. We then assessed the responses, blended related meritorious ideas, and selected additional new investment areas. The second set of six extraordinary opportunities were first outlined in NCI's Fiscal Year 2001 Budget Proposal, *The Nation's Investment in Cancer Research,* and are continued in this Proposal for Fiscal Year 2002:

- Genes and the Environment
- Cancer Imaging
- Defining the Signatures of Cancer Cells: Detection, Diagnosis, and Therapy
- Molecular Targets of Prevention and Treatment
- Research on Tobacco and Tobacco-Related Cancers
- Cancer Communications

To qualify as extraordinary opportunities, research initiatives must:

- Respond to important recent developments in knowledge and technology.
- Offer approaches to cancer research beyond the size, scope, and funding of our current research activities.
- Be implemented with specific, defined investments
- Be described in terms of achievable milestones, with clear consequences for not investing.
- Promise advances for making progress against all cancers.

In addition, these investment areas will result in new extramural grant or contract awards; collaborative efforts with other institutes, government agencies, or the private sector; and new or expanded scientific programs within NCI divisions. They promise to take us to a new era in cancer prevention and care. Although the needed resources are not trivial, our failure to respond quickly with investment in all of these areas will slow the pace of cancer research at all levels and will impair our ability to better care for those whose lives have been touched by cancer.

GENES AND THE ENVIRONMENT

The Opportunity

Conceptual and technical breakthroughs and the often breathtaking pace of scientific discovery has engendered among cancer researchers a tremendous sense of optimism that new avenues will be found to prevent, detect, diagnose, and treat cancer. Nowhere is this sense of promise greater or the potential implications more profound than at the interface of epidemiology and genetics. By marrying the study of the distribution and causes of cancer in human populations with cutting-edge genetic and related molecular technologies, we will be able to:

- Identify genes that predispose people to cancer and point to previously unsuspected environmental carcinogens.
- Study genetically susceptible subgroups to predict the slight to moderate elevations of risk that may result from their exposures to certain types of substances in the environment.
- Quantify the cancer risks associated with gene-environment interactions to enable us to guide individual and public health strategies aimed at preventing and controlling cancer.
- Design new approaches to health and cancer care based on an understanding of how genes modify and interact with environmental exposures.

The pivotal role of lifestyle and other environmental exposures as causes of cancer is reflected in the substantial variation in cancer incidence around the world and in the changes in risk observed among groups that migrate and settle in a new country. Furthermore, epidemiologic research has identified a wide range of cancer causing exposures including tobacco use, dietary components, sunlight, ionizing radiation, environmental chemicals, infectious agents, obesity, exercise, hormones, and reproductive factors.

Cancer susceptibility is another critical piece of the puzzle. For example, why does one person with a cancer-causing exposure (smoking or infection with human papillomavirus, for example) develop cancer, while another does not? Intensive study of rare cancer-prone families has provided insights into this apparent paradox. We know that disruption of fundamental cellular processes contributes to the development and progression of the more common, non-hereditary forms of cancer. Yet even among individuals who have inherited cancer-predisposing genes, the risk of developing cancer appears to be modified by other genetic and environmental factors. There is mounting evidence that a person's genetic make-up may influence susceptibility or even resistance to cancer-causing exposures. Opportunities now exist to determine how variations in these genes combine with environmental and other factors to induce cancer in the general population.

The exciting opportunities of this emerging field are accompanied by enormous challenges. Population studies sufficiently powerful to examine the complex interactions of multiple genetic and environmental factors will involve unprecedented numbers of participants and will require new research infrastructures and strategies for interdisciplinary collaboration. As we gain in our understanding of individual-specific risk factors, we must strive to ensure that this knowledge is used appropriately and is not harmful to the individual. Psychosocial, legal, ethical, and clinical

issues must be addressed, and individuals, families, and health care providers must be able to take appropriate action without repercussions.

Goal

Discover genetic, environmental, and lifestyle factors and their interactions that define cancer risk and can inform the development of new strategies for prevention, early detection, and treatment.

Progress in Pursuit of Our Goal

Today's new opportunities in the area of genetics are a direct benefit of our earlier investments. For example, NCI's Cancer Genome Anatomy Project (CGAP) has resulted in the discovery of over 44,000 new genes. New technologies have permitted scientists to determine which genes are active in normal or in cancerous tissues. There has been an exponential increase in the pace of identifying genes that maintain the integrity of our genetic material, regulate cell growth and development, and determine our response to hormones and other chemicals produced by the body as well as to environmental agents. Related discoveries have enabled us to characterize the function of hundreds of new genes and pathways. Vast public databases contain millions of entries describing gene sequences, their expression in different tissue types, and their location in the human genome. These advances are making possible a new generation of epidemiologic research that will lead to a comprehensive understanding of environmental and genetic determinants of cancer. NCI research and support activities in this area are described below.

- Establishing significant and valid evidence for gene-environment interactions requires studies of large populations over extensive periods of time.
    - In cohort studies**,** information on exposures to factors that might affect cancer risk and biologic samples are collected for individuals in large population subgroups. By systematically following these individuals over time to determine who develops cancer and who remains cancer free, scientists can compare the risk of developing cancer for those with specified exposures and genetic profiles to those without such exposures or profiles. To facilitate the efficiency and efficacy of this kind of cohort studies, NCI is establishing the **Cohort Consortium** comprised of investigators from around the world who direct cohort studies. The Consortium will facilitate the pooling of data on very large numbers of people, foster collaborative links among resources, and organize collaborative studies.
    - Case-control studies retrospectively examine exposure histories and genetic profiles of individuals who already have a cancer (cases) compared to exposure histories and genetic profiles of individuals who have not developed cancer (controls). NCI is assembling **two networks to support large-scale, case-control studies** of gene-environment interactions. One is a network of population-based cancer registries and the other a network of hospitals caring for large numbers of cancer patients.

- To better understand the cancer related gene variations that may occur more commonly in some population groups than in others, NCI has expanded the tools available to the cancer genetics community through the World Wide Web. Through the **Genetic Annotation Initiative** (GAI) of CGAP, scientists have identified more than 20,000 genetic variations, and they expect to expand that number to nearly 500,000 by 2002. Researchers are using sophisticated computer programs to identify genetic variants in individuals with cancer, to predict the likelihood of their occurring in other cancer patients, and to determine where variants occur in some patients or some types of cancer more than in others. New technology development through the **Unconventional Innovation Program** is also improving our ability to effectively analyze the large volumes of samples and data in these population-based studies.

- Members of the **Mouse Models of Human Cancers Consortium** (MMHCC) are developing and validating mouse models with heritable malignancies that parallel human disease and making them available to allow scientists to validate suspected gene-environment interactions. Composed of 20 principal investigators from institutions around the country, the MMHCC uses World Wide Web based discussion forums and other communication tools to integrate emerging knowledge about cancer susceptibility from animal models with studies on human populations. The MMHCC also supports a repository for models of key cancers caused by specific gene variants.

- We can gain tremendous insight into the risk of cancer by examining the personal and medical histories of high-risk families and investigating how cancer predisposing genes are modified by other genes and environmental factors in these families. NCI has initiated a **series of studies to address genetic and environmental determinants of risk** for familial cancers including breast, colon, and prostate cancers, and melanoma. Through the **Cooperative Family Registries** for breast/ovary and colorectal cancers, it has been possible to collect clinical, epidemiological, and pathological data as well as biospecimens for over 8,000 high-risk families. Analysis of this information may lead to targeted approaches for the prevention, detection, and diagnosis of cancer.

- New insights about genetic susceptibility, environmental carcinogens, and their potential interactions can be codified in **cancer risk prediction models** that can in turn be used to estimate individual risk. Breast cancer risk models have been employed in two large cancer prevention trials and the predictive power of the breast cancer risk model has been confirmed through validation studies. This same type of methodology can now be applied to risk prediction for other cancers.

- Clinical trials involving genetically high-risk individuals are used to increase our understanding of the clinical, behavioral, and societal issues associated with cancer susceptibility. One project in this area has been **a feasibility study of the comparative value of early screening and diagnostic tools** in breast cancer gene mutation carriers. Another such study is a pilot program for prostate cancer screening and chemoprevention in men who are carriers of susceptibility genes for breast or ovarian cancer. NCI also has begun a follow-up study of women prone to breast cancer who have previously

undergone procedures to obtain cell samples used to search for molecular fingerprints of pre-malignant cells that could be of value for early detection.

- NCI has established a **state-of-the-art bioprocessing and biorepository facility and a genotyping facility** to handle large volumes of specimens and data to support NCI efforts in molecular epidemiology. These facilities serve as prototypes for a regional network of such facilities to support molecular epidemiology studies on a regional basis.

The Plan

Objectives and Milestones for Fiscal Year 2002

1. Identify new environmental risk factors and susceptibility genes and determine their interactions in cancer causation.

- Expand the population resources in the Cohort Consortium by enhancing the collection of biospecimens. This will include adding biospecimen collections to key existing cohorts to increase the numbers of individuals and diversity of the populations covered, and developing within one cohort the systematic collection of fresh-frozen malignant and non-malignant tissue specimens to allow development of studies of gene expression and other molecular profiles.

- Fund and conduct 2 large gene-environment, case-control studies of less frequently occurring cancers. One study would be in a population-based cooperative group and the other in a hospital-based group being established for this purpose. Cancer types selected would be based on increased incidence, ethnic disparities, and geographic patterns.

- Begin development of 2 regional centers for state-of-the-art biospecimen processing and storage and for high throughput genotyping to support molecular epidemiology and other interdisciplinary studies of human cancer.

- Continue development of informatics systems to collect, store, analyze, and integrate the vast amounts of epidemiologic, clinical, and laboratory data characteristic of molecular studies.

2. Develop new ways to assess and measure environmental exposures for use in population studies.

- Continue to develop new epidemiologic methods for assessing complex exposures over a lifetime. Coordinate the use of these methods for the gene-environment interaction studies within the Cohort Consortium and other large-scale population studies of cancer.

- Further expand the NCI's Unconventional Innovation Program, Phased Innovation Award, and Small Business Innovation Research program to develop new non-invasive techniques for collecting and measuring DNA and proteins in very small amounts of biologic material and apply these techniques to studies in the Cohort Consortium and other large-scale studies of gene-environment interactions.

- Supplement ongoing research programs to develop and validate measures of the cumulative cellular, genetic, and molecular effects of exposure to environmental carcinogens in non-tumor tissue.

- Continue to expand and supplement research programs designed to develop and validate molecular approaches to define characteristic mutation patterns of DNA damage in tumor cells that implicate specific carcinogens.

- Use emerging technologies to develop molecular and immunologic techniques that will enable screening of large numbers of biologic samples to identify infectious agents relevant to human cancer.

- Continue to work with academic centers, Cancer Centers, and schools of public health to develop model training programs in molecular epidemiology.

3. Identify and characterize gene variations involved in key molecular pathways important in cancer.

- Extend CGAP's GAI efforts to identify new genetic variants relevant to cancer in clinically and epidemiologically defined populations.

- Expand the GAI's efforts to define key molecular pathways by performing comprehensive genetic variation characterizations on an extended set of gene and protein expression profiles generated by the CGAP.

4. Develop new experimental models that parallel human cancer related genes, pathways, and processes.

- Augment the MMHCC to derive and refine mouse models of human hereditary cancer genes for which models do not exist.

- Expand the MMHCC to generate valid mouse models based on epidemiologic observations of genetic and environmental modifiers of cancer risk.

- Broaden MMHCC efforts to evaluate within the collection of appropriate models the potential environmental factors to modify cancer development.

- Support use of the MMHCC mouse cancer models to discover biomarkers and *in vivo* approaches for the early detection of cancer and to develop and test new prevention strategies.

- Stimulate expansion of the portfolio of non-mammalian organisms as models of complex interactions among the pathways and processes that contribute to cancer etiology.

5. Identify cancer predisposing genes in high-risk families and investigate how expression of these genes is modified by other genes and environmental factors.

- Expand the network of cooperative registries to enhance recruitment of high risk families and foster development of shared research tools with a specific focus on informatics development and support.

- Initiate collaborative interdisciplinary studies of large numbers of high risk families to quantify cancer risk among carriers of major genes and to investigate the genetic and environmental modifiers of risk.

- Fund 2 new consortia of investigators to identify the genetic basis of familial aggregations of cancers that have not been linked to genes. The cancer sites chosen will be based on a review of evidence of the likelihood of a major gene effect, and the opportunities to study a sufficient number of high-risk families.

- Continue to expand the capacity and use of the NIH Center for Inherited Disease Research (CIDR) and other activities to accelerate cancer gene identification.

- Initiate collection of fresh frozen tumor tissue and other biospecimens from genetically cancer-prone individuals and families for microarray-based analyses of molecular signatures of cancer.

6. Refine cancer risk prediction methods/models to integrate genetic and environmental determinants of cancer.

- Augment clinical trials and observational studies of breast cancer to validate current risk prediction models and to formulate new ones. Expand the development of risk models that predict the occurrence of other major cancers.

- Expand the application of risk prediction models to target interventions aimed at cancer prevention, detection, diagnosis, or treatment.

- Extend risk models to account for both cancer and non-cancer risks and to fit ethnic and minority populations.

- Devise and test risk communication strategies best suited to patients, professionals, and policy makers.

- Create the prototype of a risk prediction model that accommodates gene-environment interactions for selected cancers.

7. Expand enrollment of genetically high-risk individuals into clinical protocols and conduct studies to address the clinical, behavioral, and societal issues associated with cancer susceptibility.

- Recruit genetically high-risk individuals into clinical studies conducted through the Cancer Genetics Network, Cancer Centers, centers of excellence, cooperative groups, and other appropriate study settings to assess the efficacy of preventive, early detection, diagnostic, and treatment interventions.

- Support research in cancer survivorship, including extension of NCI supported therapy trials, to enable long-term follow-up of cancer patients for the late effects of treatment, both physical and psychosocial, and including biospecimen collections to evaluate the role of genetic susceptibility in these outcomes.

- Continue to support behavioral research within the Cancer Genetics Network and other settings to assess the impact of predictive genetic testing and cancer risk assessment on high-risk individuals and their families and to develop and evaluate interventions that mitigate the negative consequences of genetic testing.

- Continue and expand the development and evaluation of educational tools to facilitate informed decision making about participation in cancer genetics research, genetic testing, and cancer risk reduction.

CANCER IMAGING

The Opportunity

As recently as 25 years ago, a physician or surgeon who suspected the presence of a tumor in a patient had few options: order x-ray studies to define and localize the tumor, schedule the patient for surgery, excise a portion of the unhealthy tissue for biopsy, remove the tumor, and explore surrounding tissues to determine if the cancer had spread. Over the last quarter century, refinements in imaging technology have substantially broadened the range of medical options. Imaging tests now provide much clearer and more detailed pictures of organs and tissues. New imaging technology allows us to do more than simply view anatomical structures such as bones, organs, and tumors. Functional imaging – the visualization of physiological, cellular, or molecular processes in living tissue – allows us to observe activity such as blood flow, oxygen consumption, or glucose metabolism in real time.

As we gain a better understanding of the fundamental nature of cancer, cellular and molecular imaging will be a key tool in translating this knowledge into better ways of detecting, diagnosing, and treating the disease. Using today's technology, we can identify the kinds of molecular structures/receptors that cover the surface of a tumor and use this information to predict how it may respond to certain treatments. Our ability to detect, through imaging, the molecular changes associated with a tumor cell promises to vastly improve our ability to detect and stage tumors, select treatments, monitor the effectiveness of a treatment, and determine prognosis. And, using a picture of how glucose is being used in tumor cells, we can demonstrate – without the need for a biopsy – how a tumor is responding to a recently administered treatment.

Detection and Diagnosis

The use of imaging technology already has had a lifesaving effect on our ability to detect cancer early and more accurately diagnose the disease. For example:

- X-ray mammography has revealed the presence of very small cancers in thousands of women before they could be detected by physical examination.
- Computed tomography (CT) and ultrasound now permit physicians to guide long, thin needles deep within the body to biopsy organs, often eliminating the need for an open surgical procedure.
- CT can show whether or not a tumor has invaded vital tissue, grown around blood vessels, or spread to distant organs.

As the science advances, seeing how the processes and pathways inside a cell change as the cell transforms from normal to cancerous will allow us to detect changes in people earlier, and eventually we expect to be able to visualize the actual molecular signatures of a cancer. We will be able to tell, in the radiology suite of a hospital, which genes are being expressed in a patient's cells, and we will be able to translate this information directly into better management of the disease.

Treatment

In addition to using CT and other imaging technologies to guide treatment choices, combining precise imaging techniques with radiation sources and high performance computing is significantly improving our ability to shape radiation treatments to the tumor's three-dimensional contours. In principle, imaging techniques can be interfaced with other tumor killing approaches – toxic chemicals, gene therapy, heat, and cold – to more precisely guide tissue destruction at the tumor site. Being able to distinguish between cancerous and normal tissue and deliver treatments only to diseased tissues in a minimally invasive way has the potential to minimize surgical trauma, shorten recovery time, and reduce health costs.

Goal

Accelerate discovery and development of imaging methods to identify the biological and molecular properties of precancerous or cancerous cells that will predict clinical course and response to interventions.

Progress in Pursuit of Our Goal

We have made significant strides, but much remains to be done before the full promise of the imaging sciences is realized for cancer research and care. Having laid the groundwork, we now are targeting tangible improvements in cancer detection, diagnosis, and treatment with results that will provide real benefits for people with cancer and those at risk. Several new initiatives illustrate our progress.

To foster interaction among scientists from a variety of fields to conduct multidisciplinary research on cellular and molecular imaging, NCI has established three **In Vivo Cellular and Molecular Imaging Centers** and awarded ten planning grants for additional Centers. These Centers narrow the gap between the discovery of new cancer genes and intracellular pathways and the translation of these discoveries into clinically useful, minimally invasive imaging approaches to gaining a greater understanding of cancer.

To stimulate the development of large-scale screening programs for early breast cancer detection, NCI is funding projects to assist investigators and small businesses in developing **digital mammography display and workstation technology**. In 2001, NCI will launch a clinical study to compare digital and conventional mammography.

To speed the development of new imaging methods, NCI has created the **Small Animal Imaging Resource Program** (SAIRP). Our five SAIRP centers are developing and applying a wide variety of imaging modalities that focus on functional, quantitative imaging. For example, an SAIRP-developed magnetic resonance (MR) technique can detect prostate tumors less than one millimeter in size in a mouse model. An MR technique that measures the growth of brain tumors in rats is being used to look for very early recurrence of brain tumors in children. Quantitating imaging data for small animals will lead the way to methods that can be applied in

humans. The SAIRP's progress in technology development and its usefulness as a resource to cancer researchers, particularly Mouse Models of Human Cancer Consortium (MMHCC) researchers, has been greater than anticipated. NCI is developing a **Preclinical Models Imaging Forum** to link experts in the MMHCC and the SAIRP. Information from this forum will help in developing and validating new preclinical models and in designing and testing of imaging techniques to detect human cancers.

To support the testing of new and refined diagnostic imaging methods for cancer, NCI has launched the **Diagnostic Imaging Network** in partnership with the American College of Radiology (Web site). The Network brings together imaging experts to perform a broad spectrum of multi-institutional clinical trials on imaging tools. A number of clinical trials have been launched or are in preparation, including a comparison of MR and CT in diagnosing gynecologic malignancies, the use of positron emission tomography (PET) to monitor response to chemotherapy, the value of spiral CT for detecting lung malignancies, a comparative study of digital versus conventional mammography, and a comparison of MRI versus CT for staging pediatric malignancies.

To facilitate the development of promising diagnostic imaging agents, NCI has launched the **Development of Clinical Imaging Drugs and Enhancers** (DCIDE) program. DCIDE will expedite and facilitate both the development of promising imaging enhancers (contrast agents) and molecular probes and their translation from laboratory synthesis to Investigational New Drug (IND) application. Under this program, developers of a promising diagnostic agent or probe can apply to NCI for assistance. NCI will make its preclinical development resources available to competitively selected developers in order to remove a significant barrier between laboratory discoveries and their entry into the clinic. To further aid the development of promising imaging agents, NCI is launching a DCIDE-like program to fund early trials of novel imaging probes.

To improve imaging technologies for prostate cancer detection that could enable clinicians to more accurately localize and stage a tumor and select an optional therapy, NCI has established the **Phased Innovation Award for Diagnostic Imaging and Guided Therapy in Prostate Cancer**. In 2001, several awards will be made for research to improve image-guided surgery and radiotherapy.

As we develop molecular analysis tools to expand our understanding of the biological basis of cancers, imaging applications will be a critical part of the effort. The **Innovative Technologies for the Molecular Analysis of Cancer** award provides assistance for high-resolution cellular or molecular imaging research, access to tissue samples, development of preclinical models, and the conduct of clinical investigations as an important extension of molecular analysis methods. The **Applications of Innovative Technologies for the Molecular Analysis of Cancer** awards will provide a means of piloting and evaluating newly developed high-resolution imaging technologies.

To facilitate the development, testing, and adoption of new imaging modalities and applications, NCI has organized a unique forum that brings together technology developers from academia and industry with the funding agencies, regulators, and reimbursers of technology. NCI's partners include the Food and Drug Administration (FDA), the Health Care Financing Administration

(HCFA), other third-party payers and providers, and major device manufacturers through the National Electrical Manufacturers' Association. These **partnerships** promote communication and progress in this critical area. The first forum was held in September of 1999 and the second is planned for September of 2000.

NCI, FDA, and HCFA also have formed an **Interagency Council on Biomedical Imaging in Oncology** to offer a multi-agency perspective on communicating with government for investigators and manufacturers attempting to bring emerging medical imaging technology into the marketplace. Council members have experience and knowledge concerning their particular agency's decision making processes with regard to medical imaging products and will provide advice on projects or proposals voluntarily submitted by investigators and technology developers in industry and academia. The Council will meet a few times per year beginning in July 2000.

Because partnerships play a critical role in aiding the development of new and emerging imaging technologies, NCI has formed a **partnership with the National Science Foundation** (NSF) that will stimulate research on biophotonics. In addition, plans have been laid for NSF to fund image processing research using a spiral CT lung database developed through NCI-sponsored research.

Recognizing the potential benefits to human health to be realized from applying and advancing the field of bioengineering, NCI plays a key role in the trans-NIH **Bioengineering Consortium** (BECON) which focuses on bioengineering issues and fosters new basic understandings, collaborations, and transdisciplinary initiatives among the biological, medical, physical, engineering, and computational sciences. The research and collaborations supported through BECON will aid NCI in developing imaging technologies for detecting and treating cancer. For example, NIH has created the **Bioengineering Research Partnership Programs** to support multidisciplinary research teams with bioengineering expertise that are applying an integrative, systems approach to developing knowledge or methods to prevent, detect, diagnose, and treat disease and understand health and behavior. NIH also has established the **Bioengineering Research Grants** initiative with a similar scientific scope, but designed for a limited number of investigators or institutions.

The Plan

Objectives and Milestones for Fiscal Year 2002

1. **Strengthen the foundations of imaging technologies and methodologies to assist in fundamental investigations of cancer.**

    - Fund 2 additional In Vivo Cellular and Molecular Imaging Centers (ICMIC).

    - Fund 8 to 10 supplements for collaborations between SAIRPs and other NCI programs such as the MMHCC.

- Fund 8 to 10 seed grants (R21) and 6 Phased Innovation Awards (R21/R33) for research on clinical applications of optical technologies, or integration of optical technologies with other imaging methods such as MRI and ultrasound.

2. Expand the development of novel imaging agents.

- Increase the number of imaging agents supported by the DCIDE program from 6 to 12 per year.

- Increase contract support for early clinical trials of imaging agents (safety and efficacy studies) from 8 to 12 trials per year.

- Enhance the publicly available database of imaging agents by adding information on their properties.

3. Integrate molecular and functional imaging methods into molecular target discovery, drug development, and early clinical trials.

- Fund 8 supplements for imaging collaborations with the grantees in the Molecular Target Drug Discovery (MTDD – see Molecular Targets) initiatives.

- Fund 6 to 8 supplements for development of imaging cores within the Interdisciplinary Research Teams for Molecular Target Assessment (IRTMTA – see Molecular Targets.)

- Fund imaging cores within the Molecular Target Laboratories (MTL – see Molecular Targets.)

4. Develop and use imaging as an endpoint in clinical trials.

- Fund supplements for 10 to 15 imaging cores within NCI-funded Cancer Centers to provide expertise in clinical trials that use imaging results as an endpoint.

- Support expert panels to develop consensus criteria for using imaging results as endpoints in clinical trials.

- Fund a clinical trial to evaluate the potential clinical benefit of digital mammography compared to conventional mammography.

- Fund a randomized pilot study to assess feasibility of conducting a clinical trial of spiral CT as a screening method for lung cancer detection.

- Fund a large randomized clinical study of spiral CT as a screening method for lung cancer detection if pilot study shows randomized design to be feasible.

- Fund clinical studies to: compare CT colonography with endoscopic colonography for early detection of colon cancer and polyps; evaluate magnetic resonance spectroscopy for the early detection and assessment of prostate cancer; and evaluate the role of F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) studies for staging lung cancer.

8. Accelerate the development and clinical testing of image-guided interventions.

- Fund 6 to 10 Phased Innovation Awards (R21/R33) for image-guided therapy research that emphasizes a problem-solving, organ-specific approach and promotes interactions between clinicians and bioengineers.

- Fund 4 to 6 supplements for collaborations between the Clinical Trials Cooperative Groups and the Diagnostic Imaging Network for the testing of promising, minimally invasive, image-guided interventions.

9. Develop innovative imaging technologies and conduct early clinical trials of new devices.

- Create a competitive program in which innovative equipment prototypes developed in industry and academia are provided to selected academic institutions for feasibility testing, in collaboration with the developer.

10. Establish information archives and repositories for the research community.

- Establish data banks of standardized digital image data associated with known clinical outcomes to provide a research resource for a variety of investigators.

- Fund 6 to 8 grants to develop and test image processing and analysis algorithms using these standardized data sets.

DEFINING THE SIGNATURES OF CANCER CELLS: DETECTION, DIAGNOSIS, AND THERAPY

The Opportunity

In the 19th century, the light microscope opened a new frontier in the study of disease by opening a window on the inner workings of the cell. With this instrument, pathology – the branch of medicine that deals with the essential nature of disease – expanded to include the study of structural changes in cells. For the first time, disease could be linked to visible, recognizable changes in the cells of the body.

At the cusp of the 21st century, new molecular-based technologies are bringing us to a similar revelation. These new technologies are enabling us to identify features of individual cells in ways unimagined by our 19th century predecessors. For example, all cell types, depending on their functions, have unique, identifiable "signatures" or special characteristics, such as which genes are active and what proteins or other cellular products are manufactured by the cell. Our new technologies are enabling us to read and understand those signatures.

We have learned that during the transformation of a normal cell to a cancer cell, the signature changes, and that change becomes a signal of the presence of cancer. Further, we have learned that cells surrounding an incipient tumor may also undergo changes, indicating that cancer is present. For example, tobacco-induced molecular changes in the mouth may predict the risk of developing lung cancer, and cancers of the urinary tract may be signaled by cancer cells that are "shed" in the urine. Reading the signatures of these easily accessed cells may enable us to develop simple, non-invasive tests to find cancers located deep within the body.

The implications of these findings are profound. By reading cellular signatures accurately, we may be able to detect and diagnose cancers before they have had a chance to invade nearby tissues. In fact, with the tools we are developing, a single drop of blood from a patient's finger may be all that is needed to find a cancer, assess the threat it poses by comparing its traits to profiles in an online library of tumor characteristics, choose the best possible treatment, and monitor the patient's recovery. By assessing the meaning of individual changes in the cell's signature, we will be able to determine which cancers are most likely to progress and which are less likely to do so, thereby avoiding the consequences of unnecessary treatment. By studying the sequence of changes a cell undergoes as it transforms from normal to cancerous, we will gain important insights into the etiology of the disease. And by applying what we have learned, we will be able to identify new targets, at the molecular level, for effective prevention and treatment.

"Defining the Signatures of Cancer Cells" was first identified as an area of extraordinary scientific opportunity in 1996, and it continues to be an area rich in scientific promise today. For example, we now are in a position to learn new ways to characterize tumors more efficiently – that is, to determine which genes are active and inactive, and the levels of specific proteins that are present in a particular tumor. Such "molecular fingerprinting" will greatly enhance the specificity of cancer diagnosis by allowing us to differentiate among tumors at the molecular level, and will enable us to devise treatments targeted at cellular subtypes of different cancers.

(See Spotlight on Research, p. X.) We now can use changes in molecular signatures to help us identify infectious and environmental agents that may be responsible for the development or progression of a tumor. In addition, while many of our previous efforts have centered on identifying genes involved in cancer, we are very interested in learning more about the cellular functions of the proteins produced by these genes. Finally, there has been a gap between the identification of preclinical tumor changes, early evaluation of new identification techniques, and their clinical application. We now have the opportunity to synthesize these disparate findings into a body of knowledge that will translate into real health benefits. Our ultimate goal is to push back the detection and diagnosis of cancer to the earliest stages, thereby offering the potential to focus intervention efforts at preventing overt disease.

Clearly, we have made substantial progress, but much remains to be done if we are to take full advantage of the opportunities in this area. The identification of the molecular signatures of cancer is drawing a static picture of the molecular composition of a cancer cell, providing an opportunity to begin to develop targeted diagnostics and therapeutics. However, a full understanding of the initiation and propagation of cancer will require a dynamic understanding of the process. Thus it is important to understand how alterations in a few molecules might have significant effects on a variety of cellular functions. To achieve this understanding, we need to assemble the molecular signatures information into a complete picture of the living cancer cell. In addition, the diagnostic value of molecular-based methods must be confirmed and their practical benefits established against the background of conventional medicine. New technologies must be developed, and new preclinical models must be created and validated to establish our findings. Finally, it is crucial that we develop the sophisticated computer systems, databases, and statistical methods needed to integrate the complex information being generated by the new technologies with the biologically relevant data. In this way we will be able to validate the predictive value of the new approaches.

Goal

Generate a complete catalog of the distinguishing molecular signatures of normal, precancerous, and cancer cells at all stages in all tissues, and use the catalog to develop diagnostic techniques for the earliest detection of precancerous lesions and cancers; develop signature-based therapies; and identify subsets of patients with different prognoses to predict therapeutic response.

Progress in Pursuit of Our Goal

Identifying, characterizing, and validating signatures of cancer cells will help us understand the molecular underpinnings of cancer and aid us in the earlier detection of many cancers and the selection of more targeted treatments. We are making significant progress in this area, as illustrated by these highlights.

- Each cell has an identifiable signature, a pattern of genes that are expressed and proteins that are manufactured. As a normal cell is transformed into a cancer cell, its signature

changes. To identify the changes in signatures linked to major steps of tumor development, NCI is building the complete molecular catalog of cancer through the **Cancer Genome Anatomy Project** (CGAP). Over 44,000 new genes have been discovered through CGAP's main component, the Human Tumor Gene Index. (For CGAP go to www.ncbi.nlm.nih.gov/CGAP) To help us better understand the genetic and molecular foundations of cancer and other human diseases, NIH is creating a **Mammalian Gene Collection** (MGC). The MGC will enable the scientific community to obtain individual full-length, human or mouse cDNAs for more rigorous study of individual genes, their protein products, and the role they play in many human diseases, including cancer.

- To identify, characterize, and validate signatures, and to apply this knowledge, we must continue to develop novel technologies and make molecular and analytic resources available. Through the **Unconventional Innovations Program** (UIP), NCI is supporting peer-reviewed, high-risk, high-impact ideas that have the potential to revolutionize cancer research and cancer care. Five UIP contracts for "Novel Technologies for Noninvasive Detection, Diagnosis, and Treatment of Cancer" have been awarded. The UIP is complemented by the **Innovative Molecular Analysis Technologies Program**, which has awarded over 80 grants focused on development and pilot applications of novel technologies for the molecular analysis of cancers and their host environment. NCI also is working with the National Aeronautics and Space Administration (NASA) to develop minimally invasive molecular biosensors and is sharing ideas on the development of other high-impact technologies. The agencies host the **NASA/NCI Biotechnology Forum**, a Web-based forum that brings together NCI and NASA scientists, technologists, and engineers. Finally, to identify new leads for cancer therapy and development of novel strategies for marker discovery, NCI is funding the generation of **combinatorial libraries** of small molecules, peptides, and antibodies. These libraries can be screened to identify molecules (ligands) that bind differently to tumor and normal tissues or bind differently between tumors of varying malignant potential. These ligands can provide new approaches to cancer diagnosis and prognosis.

- **Tissue resources** can aid scientists in the discovery and research application of molecular signatures to problems in cancers. Realizing the importance these resources, NCI has launched several initiatives in this area. NCI tissue resources include cooperative tissue resources for breast and prostate cancers and the **Cooperative Human Tissue Network**. The Institute is increasing access through the **Tissue Expediter**, who helps researchers locate the specimens and related clinical data they need. To improve the usefulness of fixed tissue for molecular technologies to be applied to human tissue specimens, NCI will fund research on tissue preservation. NCI also has created the **Shared Pathology Informatics Network**, a consortium of institutions connected by a model Web-based system that provides direct access to data related to specimens archived at member institutions. Tissue resources will likewise be key as we conduct tissue microarray technology research and development through the NCI and NHGRI **Tissue Array Research Program** (TARP). Tissue microarrays, which can hold hundreds of tissue sample samples on a single slide, hold great promise in the search for and validation of molecular signatures. The program will produce multi-tumor screening tissue microarrays

for the research community starting in the Fall of 2000, serve as an arraying facility for groups with unique tissue materials, and disseminate tissue microarray technology by providing training. TARP efforts will be supported by NCI's **Advanced Technology Center** (ATC) where scientists use new technologies to address biological, clinical, and genetic questions pertinent to human cancers. The ATC, which also houses CGAP, is a premier facility for developing tools for molecular expression profiling studies.

- Using experimental animal models that parallel the behavior of human cancer and its response to preventive and therapeutic interventions will greatly improve our understanding of molecular changes that contribute to cancer and could enhance our ability to evaluate biomarkers prior to clinical application. To meet this need, NCI launched the **Mouse Models of Human Cancer Consortium**, which is developing and making available to the research community characterized and validated mouse models. In addition, NCI's **Mouse Cancer Genome Anatomy Project** (mCGAP) is investigating molecular determinants of cancer in the mouse for comparative studies in human tumors. The materials developed are being made publicly available publicly to support efforts to identify mouse modifier genes involved in cancer etiology.

- A tumor cell's signature may hold the key to earlier detection of the cancer. To identify and evaluate these biomarkers and technologies for earlier detection and risk assessment of for all major cancers, NCI established the **Early Detection Research Network** (EDRN). The EDRN is a national network of academic and industry investigators with expertise in laboratory and clinical sciences, biostatistics, informatics, and public health. issues. Research funded through EDRN's 18 Biomarker Developmental Laboratories, three Biomarker Validation Laboratories, eight Clinical/Epidemiology Centers, and Data Management and Coordinating Center already is yielding results. Researchers funded through EDRN have discovered a novel approach for detecting cancer based on mutations in mitochondrial DNA found outside a cell's nucleus. (See Spotlight on Research, p. x.)

- The traditional classification of human tumors is based on tumor structure, but structure alone does not always accurately predict a tumor's biological behavior, treatment response, or prognosis. NCI is seeking a more clinically predictive and useful classification system through our **Director's Challenge: Toward a Molecular Classification of Tumors**. Investigators funded by this initiative are creating comprehensive molecular profiles of tumors using DNA, RNA, or protein-based technologies. These profiles will identify clinically important tumor subsets and will provide more informative molecular classification schemes for human cancers. To validate new approaches to diagnosis, prognosis, and prediction of response to therapy, NCI has launched the **Program for the Assessment of Clinical Cancer Tests**. The program is a major expansion of NCI efforts in this area and removes significant barriers to progress in translating new discoveries into clinical practice. It helps NCI and investigators focus on linking technological availability with clinical need.

The Plan

Objectives and Milestones for Fiscal Year2002

1. **Expand the development and availability of molecular and analytic resources.**

   - Complete the Human Tumor Gene Index of genes expressed in cells at all stages of tumor development.

   - Continue development of the Mammalian Gene Collection for full-length human and mouse cDNAs.

   - Double the number of Phased Innovation Awards to develop technologies relevant to discovering and measuring molecular signatures of cancer and precancer.

   - Expand development of biosensors for human cancer and cancer development through the UIP.

   - Continue development of databases and analytic tools for comprehensive molecular analysis.

2. **Establish and make available to researchers tissue resources to maximize the practical application of molecular signatures to problems in cancer.**

   - Establish a national tissue resource system for all major cancers, including cancers of the lung, breast, prostate, colon, head and neck, brain, soft tissue, blood, bone, the gynecologic and genitourinary systems, and childhood malignancies.

   - Develop and expand tissue repositories of precancerous lesions in all major cancers.

   - Use Phased Innovation Awards to develop tissue preservation and sample preparation methods to increase their utility and compatibility with new technologies for cancer and precancer.

   - Support tissue microarray technology development and expand the TARP system for distributing tissue and tumor microarrays.

   - Develop a Web site with query and search capability to help investigators locate appropriate national tissue repositories.

- Enhance the Web-based system to query pathology information systems including pathology standardization and agreement on common data elements.

- Provide automatic encryption features for personal identifiers associated with tissue resources.

- Develop public education materials about tissue donation for research.

3. Develop molecular signatures to study and validate animal models for human cancer.

- Complete the mCGAP to define the molecular anatomy of mouse cancer models. Link the mCGAP to the mouse phenotype and tumor databases to provide a continuum of linked descriptors of cancer.

- Enhance informatics tools to link the human and mouse CGAP data for the validation of mouse models.

- Continue developing of preclinical mouse models and support application funds to validate these models by systematic analysis and phenotyping. Use these models to validate new molecular-based approaches for early detection, diagnosis, treatment, and prognosis of cancer.

4. Support novel technology development for early detection and the determination of biomarkers of precancerous lesions and cancer.

- Expand the discovery, validation, and development of new early detection tests for all major human cancers through the EDRN.

- Develop high throughput technologies for isolating and enriching cells shed in body fluids.

- Provide supplemental funding to groups conducting prevention and therapy studies to evaluate biomarkers.

5. Validate molecular classification schemes of cancer and develop new diagnostic tests.

- Fund expanded validation programs for each major cancer site as results emerge from the Director's Challenge and other programs.

- Validate new diagnostic approaches through a Program for Assessment of Clinical Cancer Tests to provide the research community with a means to evaluate and validate signatures with possible diagnostic value.

6. Support basic research aimed at characterizing aberrant molecular interactions in cancer.

- Generate a comprehensive map of all cellular signal transduction pathways and their links to one another through a Signal Transduction Annotation Consortium.

- Support basic research efforts through expanded R01 funding of analyses of: higher order cellular architecture that may be perturbed in cancer; organization of chromosomes into chromatin and their localization within the nucleus; the structure and function of molecular machines; and structure and function of membranes.

- Develop technologies for analyzing cell-cell interactions and communication that might be perturbed in cancer by funding 10 Phased Innovation Awards.

- Develop an informatics system that will enable the modeling of dynamic and integrated cellular functions by establishing a "Virtual Cell" Consortium.

MOLECULAR TARGETS OF PREVENTION AND TREATMENT

The Opportunity

Our systematic search for drugs to combat cancer began about 60 years ago. During most of this search, our understanding of cancer has been limited by technologies available at the time – the microscope enabled us to see the structure of the cancer cell, but our ability to discern the once normal features and internal pathways that had become corrupted was incomplete. As a result, our techniques for identifying drugs to prevent or treat cancer were limited to tests that measured inhibition of cancer's development or its growth in animals or test tubes. Despite these limitations, scientists have identified drugs that, alone or with surgery, can cure some cancers in people and can significantly ease symptoms in others.

Yet anyone who has ever undergone treatment for cancer – or watched a loved one undergo treatment – knows that our ability to treat the disease leaves much to be desired. Most of the common tumors of adults – the ones that cause most of the suffering and death from cancer – do not respond well to the treatments available today. And even when these treatments succeed in shrinking tumors or eliminating them from the body, they can cause a variety of short- or long-term side effects that can have a devastating impact on a patient's quality of life.

Many of the serious side effects of cancer treatments stem directly from their non-selective nature. Until recently, we have been unable to detect the differences between the molecular features of normal and cancerous cells, and thus, a compound that inhibits the growth of a tumor cell also inhibits the growth of a healthy cell, a consequence that causes many of chemotherapy's most severe toxic effects. However, drugs that target the molecular differences between tumor and normal cells – the altered genes or proteins or the corrupted pathways – promise to be less toxic and more effective than our current drugs.

The situation for prevention is similar. The finding that the anti-estrogen drug tamoxifen can reduce the risk of invasive breast cancer suggests that cancer prevention is a realistic possibility. If we know the precise molecular steps that characterize premalignant change, we can attempt to find agents that reverse these changes or block the steps critical to the full development of cancer. This new generation of chemopreventives will be optimized and made more efficient by clinically testing the effect of a preventive on its intended target.

Until recently, scientists working to discover effective prevention and treatment agents have faced a formidable barrier: not knowing precisely what cancer is. Now, however with the evolution of molecular biology and the emergence of new technologies, we are gathering remarkable knowledge about the nature of a cancer cell and the molecular changes that occur during a tumor's development. The extraordinary opportunity before us – to discover and exploit molecular targets for cancer prevention and treatment – arises from the convergence of scientific advances in several areas: cancer biology, synthetic and biosynthetic chemistry, high throughput screening, and medical imaging.

Cancer Biology
Our evolving understanding of how molecules and pathways in premalignant or fully malignant cells differ from their normal counterparts is enabling us to classify human tumors in terms of molecular changes and also has given us a new strategy for cancer drug discovery. As our understanding of cancer biology matures, targets for prevention and therapy are proliferating. Some of these targets are molecules specifically altered from their normal counterparts. Others are revealed by understanding the consequences of the fundamental molecular changes of cancer, such as blood vessel growth to nourish tumors. Still others are normal molecular machines that take on particular significance in the context of cancer, such as hormone or growth factor systems.

Synthetic Chemistry
Traditionally, the chemicals used in anti-cancer drugs have come from nature – from tropical rain forests or organisms in the sea or the soil. Using recently developed techniques, chemists now are able to create in the laboratory enormously diverse collections of compounds. Using highly informative cancer-relevant techniques that exploit our knowledge of cancer biology, we now can screen both natural and synthetically derived chemicals for possible anti-cancer effects.

Biosynthetic Chemistry
Synthetic chemists have long been able to manipulate small molecules to produce useful medicines. The biotechnology revolution has cleared the way for biochemists to mix and match genes to design synthetic proteins. Changing proteins in cells is an important breakthrough, since proteins form the "messages" that make up communication pathways that determine a cell's healthy or aberrant behavior. Now scientists can change the messages sent by protein molecules, creating a whole new class of drugs to be tested for anti-cancer activity.

High Throughput Screening
Advances in biotechnology have made it possible to devise highly sensitive, highly efficient tests for virtually any biological process. These tests, or "smart" assays, can be used many different ways. For example, they can be used to screen cell lines and tissues for the presence of particular genes, proteins, or entire pathways, an essential step in identifying the chain of events involved in every stage of cancer development. These assays also can be used to screen potential drugs for anti-cancer effects. Thousands of compounds can be screened in this manner each week. Moreover, these assays can be performed on a micro scale with tiny quantities of material, using computer-driven robots to maximize efficiency.

Medical Imaging
Until now, imaging has been used in cancer research and care to gain information about the occurrence, size, and location of tumors. Refinements in imaging technology are allowing us to watch molecular processes within the cell unfold, as they occur, with unprecedented vividness and accuracy. Imaging techniques are being developed to tell us not only the location of a tumor but the kind of molecules it contains and how its biochemical pathways work. Further advances will have a profound impact on the testing of potential cancer interventions. (See Imaging Extraordinary Opportunity, pp. x.)

The convergence of advances in these fields presents us with the opportunity for a real revolution in the discovery and development of drugs to prevent and treat cancer. Developing drugs that target the molecular features of cancer will, within the next decade, lead to a whole new generation of cancer preventives and treatments. To ensure our success, however, we need to create conceptual and functional links among drug discovery, development, and clinical testing in ways that are completely unprecedented.

To understand why, one must consider the main questions that researchers need to pursue about a new drug's effect on malignant or precancerous cells: Does the drug kill the cancer, or at least effectively block its growth and spread? What part of the cell's complex machinery does it disrupt and how is this disruption related to its anti-cancer effect? Until now, with our incomplete knowledge of cancer, we had neither the knowledge nor the tools to address this second question. Thus, our clinical testing has focused only on the first.

It is crucial that we gather the knowledge and develop the tools to answer both of these questions. When we can, we will finally be able to address some of the most important questions in cancer therapeutics: If a drug is working well, why is it working, and if not, why not? Are we giving a person the right amount, or too much, or too little? Do we have to give people the maximum amount of a drug that they can tolerate, or can we judge the right amount by whether the drug is getting to the tumor and affecting its target? Will the drug harm the patient, now or in the future? Only when we can answer these questions will we be able to predict who is likely to respond to a particular treatment and who will not. Moreover, information from the clinic and from the laboratory will reinforce each other, providing the basis for designing of even better drugs in the future.

Goal

Accelerate the discovery, development, and testing of prevention and treatment agents that target the molecular changes underlying the various stages of cancer initiation and progression.

Progress in Pursuit of Our Goal

By identifying molecular targets research as an extraordinary investment opportunity, NCI acknowledged the importance of exploiting the molecular underpinnings of cancer in our search for effective prevention and treatment interventions. We have launched a number of new initiatives and continue to support ongoing programs to stimulate research in this critical area.

The first step in this line of research is to *identify, characterize, and validate promising new molecular targets* – a protein, receptor, enzyme, or cellular pathway essential to cancer's growth and therefore, a potentially vulnerable site in the cancer cell. By exploiting these targets, we can pursue a fundamentally new approach to cancer prevention and treatment: the development of agents that selectively take aim at these newly identified molecules or pathways and block, delay, or arrest cancer's progression. To encourage creative investigations in this area, NCI will fund **Molecular Target Drug Discovery grants** in various scientific disciplines to identify

novel molecular targets for prevention and treatment, validate the targets as a basis for cancer drug discovery, and develop tests to detect the effects of various agents on the targets. We also will support **exploratory grants** to help scientists gather preliminary data to render these projects more competitive for the regular grant funding process; **small business grants** to help launch commercial products such as tests to screen agents for their effectiveness against high-priority targets; and **supplemental grants** to enable NCI grantees to extend their active grants to include studies related to drug discovery.

Recent developments in chemistry and biology offer new paths and opportunities to cancer drug discovery. Newly developed chemical and biological combinatorial techniques are enabling scientists to create, over the course of weeks or months rather than years, millions of chemically diverse structures with potential anti-cancer effects. And biotechnology advances are enabling researchers to mix and match genes to design synthetic proteins, creating a whole new class of potential anti-cancer agents. To fully exploit this *new opportunity to synthesize or acquire large numbers of possible drug molecules,* NCI is continuing its support of six **Biology-Chemistry Centers,** two of which were funded this year. These centers represent a novel interdisciplinary program to facilitate collaborations among top researchers in chemistry, biology, genetics, and computer science for the development and refinement of robotic drug production and screening technology. The Biology-Chemistry Centers already have screened hundreds of thousands of compounds.

Another ambitious effort aimed at *developing new potential anti-cancer agents* is the **Rapid Access to Intervention Development** (RAID) program, designed to efficiently move novel, scientifically meritorious treatment interventions developed in academic settings into the clinic. Because academic institutions commonly lack the capacity to develop drugs, promising ideas and candidate molecules cannot always move forward in the drug discovery process. The RAID program is designed to place NCI's drug development resources at the service of investigators with molecules that hold promise for cancer treatment. By providing the resources needed for preclinical development of drugs and biological agents, this program removes the most common barriers between laboratory discovery and clinical testing. Products developed through the RAID program are returned directly to the originating laboratory for clinical trial testing. Fourteen projects were funded in Fiscal Year 1999 and Fiscal Year 2000 and we anticipate funding additional projects in Fiscal Year 2001.

While RAID focuses on developing promising candidate molecules to treat cancer, **Rapid Access to Preventive Intervention Development (RAPID)** will provide funding and resources to scientists working to develop agents to prevent, reverse, or delay cancer development. RAPID is designed to quickly move novel preventive molecules and concepts from the laboratory to the clinic for efficacy testing in clinical trials. RAPID will accelerate the development process for preventive agents by providing academic investigators with the contract resources needed for preclinical and early clinical drug development, ensuring the efficient translation of promising discoveries even when investigators and their institutions lack the requisite development capacity or clinical expertise. Seven projects were funded through this program in Fiscal Year 2000 and we expect to fund additional projects in Fiscal Year 2001.

The many steps involved in *turning a potential anti-cancer agent into a "drug" appropriate for human use* can take years and an investment of several million dollars. The process includes discovery, efficacy testing, development of lead agents, pharmacology and toxicology studies of the potential drug, Investigational New Drug (IND) application filing with the Food and Drug Administration, and clinical evaluation. To support the participation of small businesses in this process, NCI has established the **Flexible System to Advance Innovative Research (FLAIR)** to provide small businesses the budgets and time required to identify promising agents and develop them into drugs that can be evaluated clinically.

Molecular target drug research requires innovative tools to help scientists determine whether a potential agent actually affects an intended molecular target. *To discover, develop, and validate such tools*, NCI has set aside funding for **Interdisciplinary Research Teams for Molecular Target Assessment (IRTMTA)**. Each multidisciplinary team will focus on a critical biological process thought to contain high priority targets for cancer prevention or treatment drug discovery. They will work to develop tools, probes, assays, and imaging approaches to assess the effects of drugs on their targets.

NCI recently announced the **Molecular Targets Laboratory (MTL) initiative** that will focus intensively on developing a resource of biological assays and chemical probes for biological studies of cancer. The MTLs will emphasize the need for collaboration between chemists and biologists in an effort to produce libraries of potential anti-cancer compounds for public distribution, develop screening assays suitable for high-throughput screening of chemical libraries of potential agents, and confirm a drug's initial ability to alter the drug target in cancer cells.

The Plan

Objectives and Milestones for Fiscal Year 2002

1. **Identify, characterize, validate, and produce targets in precancerous and cancerous cells for drug discovery.** We will identify novel targets that represent critically vulnerable sites – the true Achilles heels – within cells, determine the role they play, validate their biological importance in cancer growth, and mass produce promising targets for use in testing the potential anti-cancer and preventive effects of various agents.

    - Expand the Molecular Target Drug Discovery (MTDD) program to include 10 grants in each of 3 focus areas involved in cell signaling events: cell cycle regulation, cell death and immortality, and cell invasion and metastasis.

    - In conjunction with the Mouse Models of Human Cancer Consortium, develop transgenic animal models (mice genetically altered to express human genes relevant to cancer) to verify the potential "drug responsive" characteristics of selected targets (and define their associated pathways).

- Co-fund with the National Institute for General Medical Science the expansion of technology in the National Beam Laboratories to enable researchers to rapidly determine the structure of important molecular targets, thereby permitting computer modeling of potential agents.

2. **Synthesize or acquire large numbers of diverse candidate molecules for use in drug screening efforts.** We will encourage chemists and biologists to work collaboratively to synthesize novel structures aimed at defined molecular targets in cancer cells, support expanded efforts to collect candidate agents from nature, and promote research efforts to synthesize biological agents (e.g., vaccines, recombinant proteins) directed at cancer-related target molecules.

   - Procure and distribute libraries of chemically diverse compounds to cancer drug discovery researchers, including MTDD grantees, to rapidly determine the effectiveness of these compounds against novel targets in drug screens guided by target structure.

   - Expand the collection of natural product extracts from threatened ecologic niches and previously unexplored biorealms. Increase operations to augment the library of available natural product extracts to assure a constantly renewable supply of this valuable resource. Create a centralized distribution center for formatted natural product extracts.

   - Expand support of the RAID and RAPID programs to assist investigators in producing sufficient quantities of potential biological agents for testing. Partner investigators with appropriate commercial, government, or academic production facilities.

   - Create a repository for use by researchers of public domain libraries of biological agents (e.g., peptides, carbohydrates) relevant to target cells or organs.

   - Create 2 or 3 COEs in Biologics to support approaches for designing and producing, validating, and clinically testing vaccines, viral vector constructs for agent delivery, and/or recombinant proteins directed at cancer-related target molecules.

3. **Facilitate the steps necessary to turn a promising target-directed compound into a "drug" appropriate for human use.**

   - Fund contracts to study promising target-directed compounds to determine toxicity, and if necessary, modify them to be more effective, and tolerated by patients. Information gleaned from target structure and animal model studies will assist in this process.

   - Assist small businesses in cancer drug discovery by: expanding the FLAIR program to develop novel approaches to molecular toxicology, formulation advances, and

clinical evaluation and use a RAID-like process to provide contract research resources to advance concepts.

- Expand the IRTMTA from 2 or 3 to at least 10 centers with the goal of making available, once a candidate drug molecule and target is identified, a "toolbox" to speed movement to the clinic through the definition of valid assays of a drug's effect on its intended target. Develop a formal process for NCI-funded clinical investigators to access expertise for developing assays in support of early clinical trial efforts focused at whether drugs actually affect their molecular target of reference.

4. **Facilitate partnering of academic, commercial, and government resources to promote cancer drug discovery and development**.

   - Expand from 12 to 16 the number of National Cooperative Drug Discovery Groups to facilitate partnership with industry and academia with the goal of applying a multidisciplinary approach to the discovery of novel prevention or treatment strategies.

   - Support the creation of publicly available databases and data mining tools for compound and target information. These databases and tools will provide an informatics infrastructure for MTDD and MTLs and serve as an archive for MTDD and MTL information. Sponsor yearly interdisciplinary Chemistry/Biology/Genomics/Proteomics workshops for academic and small business researchers to enhance interactions and design and build a Web-based workshop to continue such interactions.

   - Double the number of academic Phase I trials supported by NCI and promote partnering between NCI-funded centers and commercial firms with suitable test agents. Provide infrastructure to centers doing Phase I studies to allow verification of the molecularly targeted nature of drug action in early clinical trials.

   - Establish 5 new high priority Phase II trials through Specialized Programs of Research Excellence (SPORE) and Cancer Centers focusing on breast cancer, prostate cancer, colorectal cancer, other gastrointestinal cancers, other gynecologic cancers, or leukemia/lymphoma.

5. **Support for special interdisciplinary initiatives**

   - Increase resources allocated to the MTLs that will focus on developing a resource of biological assays and chemical probes for biological studies of cancer.

RESEARCH ON TOBACCO AND TOBACCO-RELATED CANCERS

The Opportunity

The numbers are truly alarming. Every day, across this country, more than 3,000 youths will begin to smoke, placing themselves at increased risk for a host of cancers – lung, mouth, pharynx, larynx, esophagus, pancreas, cervix, kidney, and bladder – as well as heart disease and a range of other conditions. Of those who continue to smoke, approximately one half will die prematurely, losing an average of 20 to 25 years of their life expectancy. And an estimated 450,000 people in the U.S. will die this year alone from tobacco-related diseases – the most preventable and costly cause of death in our Nation. The global picture is even more sobering: More than one billion people smoke worldwide and an estimated three million die annually from tobacco-related illness. By 2025, the number of deaths is expected to reach ten million per year.

These statistics illustrate dramatically that tobacco – through the use of cigarettes, cigars, pipes, and smokeless products – poses an extremely serious threat to people's health worldwide. They also underscore the urgency of addressing this threat. Evidence demonstrates strongly that people who stop smoking – regardless of age – live longer than those who continue to smoke, although their risk for lung cancer remains somewhat higher than if they never had smoked. To respond to this major threat to life and health, NCI has established research on tobacco and tobacco-related cancers as an area of extraordinary opportunity.

Developing Optimal Prevention and Cessation Strategies

Studies indicate that the majority of smokers want to stop smoking completely but struggle to quit. Most adults who smoke regret ever starting. Thus, developing strategies that prevent people from ever starting to smoke and help those who currently smoke to stop is a critical need.

In the last three decades, we have witnessed many achievements in this area of research: the development and implementation of physician training and office protocols for smoking cessation programs; the confirmation of the effectiveness of primary care medical and pharmacologic interventions; the development of effective self-help interventions; and the development of tailored interventions designed to meet the needs of individual smokers. In addition, mass media interventions capable of reaching large numbers of people with prevention and cessation messages have been developed, and strategies aimed at reaching minority, ethnic, and high-risk populations have been tested. Recent large-scale programs, like the Community Intervention Trial for Smoking Cessation (COMMIT) and the American Stop Smoking Intervention Study (ASSIST), have shown both the potential and the limitations of community and state tobacco control interventions for changing attitudes about tobacco use, changing tobacco use behaviors, and reducing the tobacco-related cancer burden. Yet we still do not fully understand the most critical elements of tobacco prevention and treatment strategies, their timing, how best to target high-risk subgroups and settings, and how to tailor messages and materials appropriately for different populations.

Identifying and Targeting Populations at High Risk for Tobacco-Related Cancers and Nicotine Addiction

We have made enormous progress in understanding the molecular factors that underlie the transformation of a normal cell to a cancer cell following exposure to tobacco carcinogens. In addition, scientists have identified many cancer-causing agents contained in tobacco smoke and shown that different tobacco products and methods of nicotine delivery influence the type and quantity of exposure to these agents.

Researchers also have determined that these multiple agents seemingly induce similar changes in a cell, regardless of the cell's location in the body. The challenge now is to learn more about how and why elements in tobacco smoke target particular genes and how tobacco-induced cellular damage initiates and promotes cancer development. Such knowledge, gained through studies using preclinical models, will help us identify precancerous lesions and markers that may predict tobacco-induced cancer. Identifying markers that detect DNA damage and other antecedents of cancer will enable us to test different prevention and treatment strategies and develop new early detection methods.

This research also could provide important insights into why some people may be particularly vulnerable to harm from tobacco. For example, women develop more lung cancers than men per cigarette smoked. Certain ethnic groups appear to be at increased risk for lung cancer as well. While the reasons for these differences are not clear, smokers with certain gene variants are more likely to be lung cancer victims. Therefore, we need to develop preclinical models that will enable us to identify the harmful variants that lead to increased susceptibility to tobacco-related cancers to help determine why some individuals exposed to tobacco are particularly susceptible to cancer, while others are spared. Using this information and knowledge of how inherited susceptibilities and tobacco exposure in combination contribute to cancer, we can develop specific prevention and detection strategies and target them to vulnerable individuals.

Increasing evidence indicates that genes interact with environmental factors to influence whether an individual will start smoking, how early he or she will start, and how difficult it will be for him or her to quit. Just as we now know more about the biological basis of tobacco-related cancers, we also have learned a great deal about the psychosocial, biobehavioral, and biological determinants of tobacco use and addiction. We know, for example, that adolescent tobacco use is tied to peer and family influences and low self-esteem. We also know that continued smoking by adults is associated with nicotine addiction, depression, and stress. More recently, research breakthroughs have provided important insights into the biological basis of tobacco use and nicotine addiction, including the role of genetic factors in nicotine metabolism. For example, researchers have identified genes that modify nicotine metabolism and regulate brain chemicals that affect the pleasurable feelings triggered by nicotine. These discoveries provide unique opportunities for studying the links between biology and behavior and will help identify preexisting vulnerabilities to tobacco use. By determining how these vulnerabilities interact with sociocultural and psychological influences on tobacco use, and by improving our ability to assess risks quantitatively, we can develop more effective prevention and cessation interventions and tailor these interventions to the people most likely to benefit from them. We also can identify

effective new drugs and combinations of already proven drugs for treating nicotine addiction. The combination of pharmacologic and behavioral tailoring may be particularly important in accelerating improvements in smoking cessation rates.

Capitalizing on Social, Legal, and Public Policy Developments

A number of social, legal, and public policy developments are converging with scientific advances to create a unique opportunity to tackle tobacco use. Public attitudes reflect decreasing acceptance of tobacco use as a social norm. Government agencies, academic institutions, and professional and voluntary organizations are making major commitments to reduce tobacco use and exposure to tobacco carcinogens. Through lawsuits, states are recovering billions of dollars lost to the treatment of diseases caused by smoking. However, while state political leaders have been urged to use these funds to expand tobacco control programs, they almost certainly will use most of the funds to address other priorities. This dilemma underscores the need for NCI to expand its investment in tobacco control research to ensure that the best scientific evidence informs state and community programs.

In summary, we have an unprecedented opportunity to reduce the enormous burden of tobacco use on our Nation's public health. The investment proposed here will enable us to gather knowledge that will inform policy makers and public health practitioners about the best strategies for preventing and treating tobacco use and tobacco-related cancers. More effective smoking cessation programs alone could save many of the nearly 160,000 lives lost to lung cancer each year. Furthermore, by expanding our efforts to understand the causes of tobacco use, addiction, and tobacco-related cancers, we can develop new and better ways of prevention and treatment, and one day stem the epidemic of tobacco-related disease and death.

About Tobacco (sidebar)

- Tobacco is responsible for more than 30 percent of all cancers and nearly one in five deaths in the U.S. every year.
- In the last decade, more than four million people in this country lost their lives to tobacco-related diseases, including, according to Environmental Protection Agency estimates, more than 30,000 nonsmokers who died of lung cancer caused by breathing smoke from others' cigarettes.
- Lung cancer deaths are still increasing among women.
- The financial costs of tobacco also are rising. Over the course of their lives, current and former smokers generate an estimated $501 billion in excess health care costs. Tobacco costs Medicare a staggering $10 billion each year and Medicaid more than $12.9 billion annually.
- The latest figures confirm a disturbing increase in youth smoking over the past decade. More than one-third (34.8%) of high school students reported using some form of tobacco in the past month.
- Adult smoking rates did not decrease from 1995-1997, but smoking increased among those 18 to 24 years of age.

Goal

Understand the causes of tobacco use, addiction, and tobacco-related cancers and apply this knowledge to their prevention and treatment.

Progress in Pursuit of Our Goal

NCI has initiated a broad range of projects directed at understanding the biological, behavioral, and societal bases of tobacco use and addiction and the relationship between tobacco exposure, genetic susceptibility, and cancer. These projects are informing the development of more effective prevention and treatment strategies.

In an effort to better understand the causes and mechanisms of tobacco-related cancer, NCI has a number of projects underway. Within its intramural program, NCI is conducting large case-control studies of lung, bladder, renal, non-Hodgkin's lymphoma (NHL), biliary tract, and gastric cancer that include genetic and biomarker components to complement traditional epidemiological approaches for assessing risk. Population-based cohort studies on cervical cancer and lymphomas and leukemias and the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer study will assess screening strategies for multiple smoking-related cancers as well as colonic polyps, a preneoplastic condition related to tobacco. A study of family members with Von Hippel-Lindau (VHL) syndrome, an inherited cancer syndrome, is establishing whether tobacco influences cancer in cancer-prone families. To advance our understanding of genetic and environmental interactions that influence smoking behavior and lung cancer in particular, NCI will support a **genetic epidemiology of lung cancer and smoking study**. This interdisciplinary case-control study will explore how tobacco and genes influence both lung cancer and smoking by incorporating the study of siblings and an extensive biospecimen collection. (See Extraordinary Opportunity on Genes and the Environment for a discussion of related studies and supportive infrastructure, including biorepository, bioprocessing and high throughput genotyping facilities.)

Seven **Transdisciplinary Tobacco Use Research Centers** (TTURCs) are helping to provide the needed infrastructure for tobacco research across disciplines, an effort that will greatly enhance our understanding of tobacco use, addiction, and tobacco-related cancers. Advances in molecular biology, pharmacology, and behavioral science provide opportunities to study the tobacco problem in ways that will integrate biological and psychosocial models of tobacco addiction. The TTURCs, a joint program of NCI, the National Institute on Drug Abuse (NIDA) and the Robert Wood Johnson Foundation, are providing a unique environment for collaborations of scientists across many disciplines. TTURC researchers are tackling a wide range of topics, including genetic susceptibility, animal models of behavior, sociocultural factors, and innovative treatments. These centers will accelerate development of effective tobacco control interventions, speed the transfer of these approaches to communities across the Nation, and train a new generation of tobacco control researchers.

To further understand youth tobacco use and addiction, NCI, in collaboration with a number of other NIH Institutes, is supporting a variety of research projects resulting from a solicitation inviting **youth prevention and cessation research**. Projects now underway are addressing prevention, experimentation and onset of regular tobacco use, dependence and withdrawal, and cessation and treatment of tobacco use by adolescents. The results of these studies will provide the critical scientific evidence needed to develop more effective tobacco use prevention programs.

To address the rise in the number of tobacco-related deaths among U.S. women, NCI is supporting several **studies on tobacco use and addiction among women.** Several studies focus on reducing tobacco use by pregnant women, including studies to help low-income women quit, to test the ability of women's partners to assist them in quitting, and to prevent relapse after delivery. Another study examines the relationship between smoking and major depressive disorder, a problem that disproportionately affects women. NCI is also funding a major study of African American women's health that includes an examination of smoking behavior in this population. Other studies are aimed at using moderate intensity exercise to help women quit smoking, using an integrated public health intervention to promote cessation among under educated women smokers, and examining the relationship between smoking and cervical cancer.

Many questions remain concerning the design and implementation of optimal state and community tobacco control programs. To address these questions, NCI is supporting 12 new **research projects on innovative tobacco prevention and control interventions at the community, state, or multi-state level.** Among the questions these projects are addressing are: What is the impact of a large tobacco control media campaign on tobacco use behaviors, readiness to quit, and attitudes toward tobacco advertising and tobacco use? How should media and policy interventions be tailored to influence high-risk groups, such as heavy smokers, multicultural groups, and youth?

NCI is working collaboratively with public and private partners to build a comprehensive and integrated surveillance system to monitor tobacco control progress at the local, regional, and national levels. NCI is supporting the expansion of two major research data resources for tobacco control surveillance research. In the first, the **Tobacco Use Supplement to the Current Population Surveys**, final data from the 1990s are to be made available by the Census Bureau in the Fall of 2000 as a public use data resource. (http://www-dccps.ims.nci.nih.gov/ARP/RiskFactor/tobacco.html) NCI will encourage researchers to analyze these data by funding supplements to existing tobacco control grants. In a second initiative, NCI is beginning pilot work to determine the best approach to creating a public use research resource of regional, state, and local tobacco related policy and legislation to expand capacity to examine the effect of these factors on regional and local tobacco control progress.

Effective communication and dissemination of information about emerging public health issues in smoking and tobacco use control are critical to reducing tobacco use among both adults and youth. NCI established the **Smoking and Tobacco Control Monograph** series in 1991. Recent data from the Tobacco Use Supplement have been used extensively in this monograph series, such as *Cigars; Health Effects and Trends, State and Local Legislative Action to Reduce Tobacco Use,* and *Changing Adolescent Smoking Behavior*. Smoking and Tobacco Control

monographs can be viewed on NCI's Web site at http://rex.nci.nih.gov/NCI_MONOGRAPHS/LIST.HTM.

In August 2000, the NCI cosponsored and participated in the **11th World Conference on Tobacco or Health,** a meeting that brought together researchers, clinicians, public policy officials, tobacco control advocates, public health workers, and educators from around the world. Held in Chicago, Illinois, and marking the first time in 25 years that this international conference was held in the United States, it show cased the state of the art in tobacco control around the world and served as a forum for sharing ideas and developing consensus on global approaches to tobacco control.

The Plan

Objectives and Milestones for Fiscal Year 2002

1. **Expand efforts to define the biological, behavioral, and social bases of tobacco use and addiction.**

   - Develop and implement specialized surveys and incorporate biospecimen collection in cohort studies to better understand youth tobacco use and addiction.

   - Establish regional repository resources to house large numbers of biospecimens and encourage collaborative studies so that researchers can identify genetic predisposition for tobacco use and addiction.

   - Conduct national tobacco control surveys through supplements to the Current Population Survey to collect information on activities that impact tobacco control. The data, covering diverse populations, are used increasingly by Federal and non-Federal researchers to examine progress in cancer control.

   - Create a public use research resource of regional, state, and local tobacco-related policy and legislation to expand capacity to examine the effect of these factors on regional and local tobacco control progress.

2. **Accelerate progress in understanding the relationships among tobacco exposure, other exposures, genetic susceptibility, and cancer.**

   - Expand existing prospective studies by incorporating biospecimens, developing standard measures and shared data instruments, and supporting cooperative efforts in order to identify and characterize genetic and biological factors affecting vulnerability to tobacco-related cancers.

   - Fund innovative studies to determine how tobacco use contributes to cancers other than lung and oral cancers, such as pancreatic, cervical, kidney, and

bladder cancers.

- Support the development of animal models for tobacco-related carcinogenesis.

- Support research that combines population and family approaches to better understand the interplay of genes and environment in tobacco-related cancers.

- Collaborate with other NIH Institutes to support studies to further define the adverse health effects of environmental tobacco smoke exposure.

2. Develop, test, and disseminate more effective interventions to prevent and treat tobacco use and tobacco-related cancers, especially in high-risk individuals and groups.

- Support pilot projects that incorporate biomarkers to develop and evaluate chemopreventive agents in populations of former smokers at high risk for developing tobacco-related cancers.

- Support the development of biomarkers of tobacco exposure and risk. Such correlative laboratory projects will complement activities ongoing in the Early Detection Research Network.

- Fund studies to develop and test new behavioral, pharmacological, and combination therapies to treat nicotine dependence, with special emphasis on populations at high risk.

- Support rapid, standardized evaluations of current tobacco cessation programs for adolescents and young adults.

- Support studies in collaboration with public and private tobacco research funding organizations to identify successful tobacco use prevention interventions.

- Expand support for research to evaluate the impact of new state and community tobacco control programs.

CANCER COMMUNICATIONS

The Opportunity

We are in the midst of a communications revolution unparalleled since Gutenberg introduced movable type to the western world in the 15th century. At no other time in history has it been so easy for so many people to access such a vast wealth of information. In particular, the Internet has multiplied exponentially our ability to make large amounts of information available to a wide audience quickly and easily.

From primary prevention to survivorship and end-of-life issues, communication empowers people to make informed cancer related decisions and to engage in behaviors that will improve their health. The Science Panel on Interactive Communication and Health convened by the Department of Health and Human Services concluded that few other health related interventions have the potential of interactive health communications to simultaneously improve health outcomes, decrease health care costs, and enhance consumer satisfaction. Scientists and communications experts who have studied the process of effective communication and its impact on health for more than 25 years have produced increasingly refined theories of health communication, including those that focus on how people process health information and how they respond to cancer related risks. We have been able to apply our increased understanding of communications to interventions that have contributed to declining smoking rates among many groups in the United States, to the increasing proportions of Americans who are eating more fruits and vegetables each day, and the larger numbers of people who are getting screened for breast, cervical, prostate, and other cancers.

Despite our progress in refining health communications theories, major gaps remain in our understanding of how consumers use health information. We must learn how to help people distinguish important from insignificant health risks and deal with contradictory health messages so that they can make informed choices. We must provide accurate and balanced information about all areas of cancer treatment and care, including complementary and alternative therapies. We must find the best ways to inform doctors of emerging best practices in patient care. And we must find ways to help health care providers be more effective communicators and integrate cancer communications into all aspects of cancer care. We need better cancer communications to narrow the enormous gap between what we know and what we do at all levels and reduce cancer related health disparities among people in vulnerable, high-risk populations. We need more research at all levels to achieve the potential of cancer communications. All this will require that we build the cadre of both health communications scientists and practitioners to conduct research and apply research results.

The National Cancer Institute, its grantees, and contractors have long been leaders in health communications. Now it is time to take advantage of new knowledge about health behavior and new technology and stretch beyond what we have ever done before, if we are to further reduce the burden of cancer. If NCI takes the lead now, we have the opportunity to use both proven strategies and new communications technologies to help people increase their knowledge, enhance their ability to negotiate the health care system, understand and modify their health risk

behaviors, and speed the pace of discovery by increasing patient access to and participation in clinical trials. Through these efforts, we will have a far richer understanding of how people use communications technologies of all kinds, and we will use that understanding to improve outcomes in cancer prevention, early detection, treatment, and survivorship.

The Changing Scene for Cancer Communications (sidebar)

Changes in the role and accessibility of information are altering health care practices, patient-physician relationships, and the way consumers and patients acquire and use information. Where once physicians were the main source of health information, now many consumers are actively using a variety of information sources to meet their needs. In the 21st century, consumers and professionals will have a host of new opportunities for creating, distributing, and acquiring health information from sources such as the World Wide Web, electronic mail, individually tailored print and multimedia materials, interactive computer games, interactive kiosks, and wireless pagers. These "new media" have already had an enormous impact as evidenced by the fact that:

- Home computer and Internet use are on the rise. In 1998, 42.1% of U.S. households had at least one personal computer, a 5.5% increase over 1997, and 26.2% used the Internet, a 7.6% increase over the previous year.
- A 1999 Harris Poll found that approximately 70 million or 74% of adults who use the Internet searched online for health information. Cancer was the third most sought-after health topic.
- In 1998, 1.9 million pieces of e-mail were processed each week by cancer related listservs (e-mail groups devoted to a specific topic) hosted by the Association of Cancer Online Resources.

Substantial barriers still prevent major segments of the population from seeking and/or using cancer information. Some people continue to lack access to the array of cancer communications media. Others are faced with content that is unintelligible to them (i.e., in the wrong language or in language that is too complex), culturally inappropriate, or simply ineffective. It is now clear that there is a "digital divide." Those who lack access to information and new online tools – the information "have nots" – are more likely to be poor, have less than a high school education, and be ethnic minorities. How can we promote the demand for, access to, and use of cancer information, given the high national rates of medical illiteracy? How can we ensure that cancer communications are salient, accurate, relevant, and culturally sensitive to diverse audiences? How can we better design our interventions to be user appropriate and to know what does not work and why? How can we help physicians and other health care providers to maximize their communication about cancer? How can we redesign information systems so they give people the information they want how, when, and where they want it? How can we help to overcome the digital divide?

New information technologies must complement, not replace, older but effective strategies, such as the mass media, one-to-one counseling, and targeted print communications. For example, most people still want to talk directly with a knowledgeable and supportive person. Such

interactions can enhance outcomes of and satisfaction with care. As we develop new technologies, we must not lose sight of the importance of personal interactions and the need for continuing research and practice to strengthen one-to-one communications. Increasingly, consumers, patients, and health professionals alike are coming to expect seamless, integrated, accessible, tailored communication choices. They want to move easily among these choices -- for example, to go from a Cancer Information Service information specialist to CancerNet or to talk to the specialist while viewing a Web site.

To be effective, cancer communications must be integrated into the cancer continuum – from prevention through treatment to survivorship and to end-of-life issues, including palliative care and pain management. Communication should be an integral component of quality cancer care. The National Cancer Institute is committed to improving knowledge about, tools for, access to, and use of cancer information for all, regardless of race, ethnicity, health status, education, income, age, gender, or geographic region.

Fundamental Assumptions of Cancer Communications

- Proactive communication strategies are needed across the cancer continuum and an individual's life span to rapidly accelerate a reduction in the cancer burden.
- A successful strategy requires that we reach a broad cross-section of the U.S. population.
- NCI's cancer communications should be based on scientific evidence obtained through high quality research, and its products should be evaluated for efficacy, impact, and use by the target audiences.
- Improving access includes removing cost barriers and enhancing ease of use, familiarity, cultural appropriateness, and appeal of the medium.
- Comprehension is essential, and messages must be perceived as salient, appropriate, and relevant.
- We must offer a flexible and adaptable menu of communication choices to reach the public, patients, underserved populations, survivors, and health care providers in diverse settings.
- The new media should complement more traditional media such as print, television, radio, the telephone, and one-to-one interpersonal communications.
- We must forge effective partnerships – e.g., with other NIH Institutes, the Centers for Disease Control and Prevention, voluntary health organizations such as the American Cancer Society, and other advocacy and self-help groups.
- Partnerships with industry and academia are essential to identify and gain access to emerging communication technologies. These partnerships should include computer, telecommunications, pharmaceutical, insurance, and new media companies.

Goal

Increase our knowledge about, tools for, access to, and use of cancer communications by the public, consumers, patients, survivors, and health professionals – with a special focus on diverse populations – to accelerate reductions in the U.S. cancer burden.

Progress in Pursuit of Our Goal

With this Extraordinary Opportunity, NCI will be able to expand our understanding of cancer communications through advanced research endeavors, to examine new technologies and tools for communications, and to apply research results and technologies to all of our internal and external communications activities. Our ultimate goal for all of our communications activities is to accelerate reductions in the U.S. cancer burden. NCI is currently carrying out several **research initiatives and other projects** to increase our knowledge about, tools for, access to, and use of cancer communications by diverse populations. We are:

- Taking the lead for the **first nationally representative survey** of the American public's access to and use of cancer related health information. This effort is under development with guidance from representatives of other Department of Health and Human Services groups including the Centers for Disease Control and Prevention, the National Institute for Occupational Safety and Health, and the National Library of Medicine as well as a number of national experts in health communications. At present, there is no national source for such data especially about underserved populations.

- Conducting research projects on how to maximize effective cancer communications through **message tailoring** and how to increase the impact of behavioral counseling on cancer control interventions.

- Funding, in collaboration with the Agency for Healthcare Research and Quality (AHRQ), an effort to review the research evidence on **cancer related "decision aids" –** interventions designed to help people make specific and deliberate choices by providing information on options and outcomes specific to a person's health status. One outcome of this project will be materials that health care providers can use to enhance their consultations with patients, especially those from vulnerable populations, about cancer related health decisions.

- Co-funding with AHRQ a program called **Making Quality Count for Consumers and Patients** to sponsor demonstration projects for developing, testing, and evaluating strategies for providing consumers and patients with information on quality that can assist them with making health care choices.

- Putting in place a mechanism for creating **Centers of Excellence in Cancer Communications Research**. The Centers will facilitate rapid advances in knowledge about cancer communications and develop, implement, and evaluate strategies to improve access to and the efficacy, effectiveness, and dissemination of cancer communications. By assembling interdisciplinary teams of researchers committed to research on important health communication questions and ensuring adequate infrastructures, we can speed the process of discovery and its application.

New technologies now make it possible for NCI to develop the tools to systematically track sources of and disseminate information about cancer to all who need it. Several NCI initiatives support implementation of an **integrated cancer knowledge management system**:

- A new **Publications Locator** enables users to view and order NCI publications online from the NCI Web site. Users have access to publications on various types of cancer, treatment options, clinical trials, genetics, risk factors and causes, prevention, and testing. Publications on managing side effects and pain also are available.

- The **Cancer Information Service (CIS) Intranet system** provides regional CIS offices with online access to NCI resource materials, fact sheets, and updates as well as the Physicians' Data Query (PDQ), all critical to the CIS mission of providing the best information possible to the public.

- Pilot projects are underway to develop an **online Cancer Information Service (eCIS)** that would provide yet another alternative for people to get answers to their questions about cancer and cancer research findings. Other similar pilot tests are planned.

Unequal access to cancer information is a critical issue for cancer communications, especially access to information available through the Internet. In 2000, NCI will provide supplemental funding, in conjunction with our Cancer Information Service regional offices, for "**Pilot Research to Overcome the Digital Divide (PRODD)**. These pilot projects will provide the foundation for larger scale projects to address the specific information access needs of underserved populations.

NCI's Operation J-O-L-T (**Joining Organizations with Leading Technologies**) is working with numerous other groups to bridge the gap between emerging technologies and their application to cancer communications. NCI coordinates activities with the World Wide Web Consortium on Cancer, a working group of cancer related Web site technical specialists and Web masters, to collaborate, share information, and support one another to deliver authoritative cancer knowledge via survivor-run and other Web sites. We have arrangements with commercial online vendors, including a large book company and a greeting card company, to disseminate to their customers information on NCI resources, publications, and the Cancer Information Service hotline at 1-800-4CANCER. We are working with a provider of Internet access hardware and software for low income families to add cancer information to their portal on the Web and with a maker of novel devices for inexpensive Internet access to include links to NCI resources directly on the devices and to develop custom versions for use by cancer patients. We are supporting major employers in establishing cancer information links through computers they provide their employees for home use. We also are working with the Open Source community, to alert software developers to the unique needs of people who use the Internet to find valid, understandable information resources and with a publisher to produce and disseminate an NCI-funded book on tailored health communications.

NCI has established a lecture series and supports a number of creative meetings and workshops on cancer and health communications related topics. The **Eleanor Nealon Extraordinary Communicator Lecture Series** pays tribute to outstanding communicators who have advanced

the science of communication or the communication of science through their professional or personal experiences. The **Breast Cancer Risk Communication Workshop** was held in collaboration with the American Cancer Society to establish standards for future risk communication initiatives concerning breast cancer. This collaboration was strengthened by a national conference sponsored by the NCI on cancer risk communication, the results of which were published in the Journal of the National Cancer Institute. A meeting on **Media and Health Education** for leading media education and public health researchers, held in collaboration with Rutgers University, identified future research directions for media education and for media interventions aimed at public health threats to youth. The **Future of Health Technology Summit 2000**, hosted in conjunction with the Massachusetts Institute of Technology, brought together creative thinkers to develop a vision for the future of health technologies, the best way to allocate research and development resources, and how to define the health technology agenda for the 21st century. The **Kentucky Conference on Health Communication**, which NCI co-sponsored with the University of Kentucky, focused on finding ways to integrate various disciplinary approaches to health communication. Individuals from relatively similar disciplines such as communication and psychology and seemingly disparate disciplines such as communication and genetics met to discuss innovative and creative ways to work together. The **Strategic Education and Training in Health Communication** (StrETCH) workshop, hosted by the NCI, convened faculty and deans of schools of public health and communications to discuss inter- and intra-institutional collaborations in health communications research and curriculum/training development. And the **Implementation of Risk Communication Efforts** workshop, sponsored jointly with the Centers for Disease Control (CDC), focused attention on the importance of initiating, delivering, evaluating, and following up on cancer risk communications.

We established a new Office of Communications in May 2000 to provide a comprehensive, integrated, and technology based communication structure that will enhance the effectiveness of our interactions with the public. New organizational units will enhance our capabilities in Web design and evaluation, maximize our use of emerging technologies, optimize our ability to help people with cancer inquiries to navigate through the NCI communications structure, and increase our readiness to form partnerships with outside organizations including consumer advocacy groups, professional organizations, and Federal/State/local health agencies.

The Plan

Objectives and Milestones for Fiscal Year 2002

1. **Support cancer communications planning, research, evaluation, dissemination, and marketing by establishing new data collection and analysis strategies.**

    - Sponsor a biennial survey of a nationally representative sample of the U.S. population to collect baseline and longitudinal data on the public's knowledge about cancer and its prevention and care; perceptions about cancer risks; and use of and preferences for different kinds of cancer communications (e.g., health care providers, mass media, Internet, NCI Cancer Information Service).

    - Access relevant commercial data on use of the new media for health communications to inform NCI's planning and evaluation efforts about which audiences use which new media and how they use them.

2. **Accelerate research and development in cancer communications by supporting Centers of Excellence in Cancer Communications Research.** These Centers will interact and be synergistic with other NCI funded centers, such as the Comprehensive Cancer Centers, Transdisciplinary Tobacco Use Research Centers, the NCI Cancer Information Service (CIS), and Special Populations Networks for Cancer Awareness, Research, and Training.

3. **Develop a menu of communication choices to meet the needs of all users and especially to increase the demand for, access to, and use of these choices by diverse populations.**

    - Conduct a series of pilot tests to explore the feasibility of these new directions, using different CIS offices and Cancer Centers as test beds.

    - Develop new communication products such as practical tool kits and decision aids to facilitate cancer communications for diverse audiences including the public, patients and their caregivers, underserved populations, advocacy groups, health professionals, and cancer communicators. Continue to work with AHRQ to fund research on decision aids and fund workshops and seminars to promote dissemination and use of these practical tools and to solicit information concerning current levels of and barriers to use.

- Fund research projects to overcome the digital divide by increasing access to and use of online and other interactive cancer communications. Support PRODD competitive grant supplements (through P30 and P50 grants) to conduct pilot research projects to overcome the digital divide in their regions.

4. **Increase the Nation's capability and capacity for cancer communications by training the health communications scientists, researchers, and practitioners needed to achieve our scientific and health communications objectives.**

   - Encourage the development of interdisciplinary training programs that, at a minimum, include people in health behavior, marketing, engineering, communications, public health, and medicine.

   - Fund existing health communications research laboratories to conduct intensive training programs and provide opportunities for research professionals in growing areas, including risk communications and interactive health communications. These will include intensive short-term training programs, R25s for interdisciplinary training, and distance learning programs.

5. **Continue to integrate and restructure NCI's communications activities to provide a comprehensive, technology supported capability for imparting information about cancer and NCI that is reliable, timely and appropriate.** We will modernize the NCI infrastructure to facilitate communication of strategic priorities, promote evolving brand identity, and effectively disseminate the results of research; adopt newly developed communications technologies and deploy them to create more comprehensive and sophisticated approaches to cancer communications; and ensure that NCI staff are knowledgeable in new technologies and ready to play a leadership role in disseminating cancer information to the public.

   - Create new communications programs and expand existing ones to apply new technologies for disseminating cancer-related information to a variety of audiences. Enhance the accessibility and user-friendliness of NCI's databases and Web sites. Focus on Web design and evaluation to enhance the effectiveness of computer-based information systems and intensive training for NCI staff. Discover and implement more effective ways to present scientific information to the public. For example, we will develop a Web-based magazine for cancer research using a multi-media approach and a search and navigation ("instant messaging") support system to allow Web users to hold live text-based conversation with NCI-supported service agents.

- Centralize the coordination of external and internal communications activities to maximize proactive responses to communications priorities and challenges. Establish a new communications coordination program to provide issue management capabilities for the Institute, linkages with NCI scientific programs and staff, and science communications expertise in broad topical areas of recurrent interest. This program will ensure maximum accessibility by the public to NCI's information resources and products and ensure the promotion of NCI's brand identity.

NCI's Challenge:
Building Our Capacity for the Future

As we move into the 21st century, we are well positioned to make dramatic improvements in human health and continue the fight against cancer. In the 20th century, we made remarkable gains in our knowledge of cancer biology. Molecular-based technologies dramatically expanded our insights into the steps involved in the transformation of cells from normal to precancerous to cancerous, allowing us to detect and diagnose cancers much earlier. New and enhanced imaging tools and techniques coupled with new drugs, targeted therapeutic interventions, and new insights and discoveries into the fundamental nature and causes of cancer present unprecedented opportunities.

The challenge before us is to build and continually enhance an infrastructure that will allow the scientific community to apply these discoveries and emerging technologies to the field of cancer research. We need mechanisms that will promote and reward innovative thinking, the cross-fertilization of ideas among disparate scientific disciplines, and enhanced collaborations among government, academia, and industry. We must develop and maintain the cadre of trained scientists from the variety of disciplines needed to undertake this essential work. And we must address special societal concerns that impact our Nation's ability to provide the best possible care to cancer patients and to ensure equal access to information, to care, and to research opportunity.

NCI's role is to provide the vision, creative environments, and diverse resources needed to ensure a smooth flow between the increasing number of discoveries and advances in cancer research and the scientific community's ability to apply these findings to prevent and treat the many forms of cancer. Yet if the pace of discovery is like an eight-lane highway, our current ability to translate those discoveries into clinical application is still much like a country road. Where the two meet, a bottleneck still prevents a tremendous number of good ideas from moving forward. Our challenge is to continue to expand the country road to the eight-lane highway that can move discoveries swiftly to their application in interventions across the cancer care continuum. To respond to this challenge, we identified six key areas for investment in our 2001 Proposal and will continue these in 2002:

- Investigator-Initiated Research
- Centers, Networks, and Consortia
- National Clinical Trials Program
- Informatics and Information Flow
- Studying Emerging Trends in Cancer
- Training, Education, and Career Development

As we move to expand that country road, there are other barriers to our overall success that we need to address. These issues of special concern are the quality of cancer care and disparities in access to information, patient care, and research opportunities and careers. We are adding two new challenge areas for 2002 to address these needs:

- Quality of Cancer Care
- Reducing Cancer-Related Health Disparities.

Addressing each of these challenge areas will make a unique contribution to our fight against cancer.

INVESTIGATOR-INITIATED RESEARCH

The Challenge

Investigator-initiated research -- research conceived and conducted by scientists in laboratories and clinics across the country and at NCI -- is the wellspring of scientific discovery. Funded and sustained by a variety of NCI grant mechanisms, our investigator-initiated research is continually yielding discoveries and insights into the mechanisms and causes of cancer and its prevention, detection, diagnosis, treatment, control, and survival.

Because of our continued national commitment to cancer research, we now are beginning to understand how cancer develops and progresses at the molecular level and how to use this knowledge to effectively prevent, diagnose, and treat cancer. We now must not only maintain our current momentum but must push forward as quickly as possible with critical research and the application of findings to prevention and treatment interventions. The pace and absolute number of our discoveries and the speed with which we can bring them to bear to benefit people, are directly linked to the resources available to support the exploration of new leads across the cancer research continuum. We must:

- Expand our research portfolio to include a greater number of research proposals that may be somewhat risky, highly speculative, or that pursue novel paths.
- Continue to expand the translational research that converts basic science discoveries into practical, affordable, and effective ways of restoring cancer patients to health and preventing cancer throughout our population.
- Create mechanisms that link basic, clinical, and population-based research with state-of-the-art resources and technologies; promote collaborations among researchers inside and outside of cancer research; and draw into cancer-related research scientists from allied fields such as chemistry, biology, physics, engineering, and mathematics to galvanize their complementary knowledge to most quickly answer the crucial questions in basic, clinical, population, and translational research.

The Nation waits eagerly for the day when cancer is no longer a threat to health and life, when most cancers are prevented, and when those that occur are cured or controlled rapidly and successfully. To meet this challenge, we must:

- Fuel the drive toward discovery by increasing our support of innovative research and providing the support needed to exploit the discoveries it yields.
- Bring to bear the best of our developing knowledge, along with the best ideas and technologies to address the full spectrum of cancer research questions – from basic research to prevention and patient care.

Continued investment in this crucial aspect of the research infrastructure will span the gap between discovery and application and transform the processes by which we bring discoveries to the benefit of people.

Goal

Speed the rate of discovery and accelerate the application of those discoveries to the population by expanding and facilitating researchers' access to resources and new technologies

Progress Toward Meeting the Challenge

Over the past four years, NCI has increased substantially the number of investigator-initiated grant applications funded. In 1995, the overall success rate for grants funded from the RPG pool was 23 percent. In 2000, we anticipate funding more than 1,230 new and competing grant applications from the Research Project Grant (RPG) pool, for an overall success rate of 29 percent. This increase has resulted in and will continue to yield substantial research rewards, but this improved funding level is still insufficient to support the wealth of innovative, high quality proposals received each year. As we achieve success in attracting new researchers to the cancer problem, the number of excellent applications is expected to grow.
(See http://www.nci.nih.gov/admin/fmb/2000Funding.htm for information about NCI-supported funding opportunities.)

To encourage the development of new technologies and innovative approaches to areas with special needs, NCI has implemented several new or expanded mechanisms. Some of these mechanisms are described below.

- The **Quick-Trials** program promises to speed the translation of ideas developed in the laboratory to early stage clinical trials by simplifying the grant application process and providing a rapid turnaround from application to funding. Initially developed as a pilot program in prostate cancer, this successful initiative has been expanded to address all cancer sites and provide funding to test and develop novel cancer therapies.

- The **Phased Innovation Awards** program, developed initially to support novel technology development for molecular analyses of cancer, will be broadened in scope in 2001 to fund projects to advance imaging technology. In addition, the Institute has expanded the Award to include a follow-on application phase -- the Phased Technology Application Award -- to ensure subsequent development towards an applied result. Seven grants were funded through this program in Fiscal Year 2000.

- In 1999, NCI used the **Administrative Supplements for Advanced Technologies** awards to fund over 20 centers focused on developing DNA array technology cores. These grants promise to make this exciting technology available to hundreds of investigators at least a year earlier than otherwise would have been possible.

- Through a **special exceptions process**, NCI ensures that new investigators share the same success rate as more established R01 applicants. In addition, the **Accelerated Executive Review** process ensures rapid reconsideration of applications ranked within a few percentile

points of the payline, especially those involving patient-oriented research. In Fiscal Year 2000, over $35 million has been spent on exceptions and more than 100 investigators benefited from these initiatives.

The Plan

Objectives and Milestones for Fiscal Year 2002

1. **Increase our investment in research to ensure a higher and sustainable success rate for competing grant applications.** Today, NCI funds just under 30 percent of competing grant applications in the Research Project Grant (RPG) pool. Yet, many innovative research applications cannot be funded and many promising ideas cannot be pursued due to limitations in resources currently available to us.

    - Fund 40 percent of competing applications, including those that have the highest scientific merit, carry great risk but may yield potentially greater reward, are unconventional but hold unique promise, are in areas of extraordinary need in specific fields of investigation or model systems, or encourage new investigators.

2. **Encourage investigators to commit to careers in cancer research and to propose more innovative and higher risk/higher reward projects.**

    - Continue to allocate the first 80 to 90 percent of available RPG funds to competing applications that fall within conventional merit rank order paylines.

    - Ensure that applications that are particularly innovative and high risk/high reward have a reasonable funding rate by identifying such research and using exceptions funding and special competitions as warranted to maintain a comparable overall success rate.

3. **Enhance the pace of high priority targeted research objectives by searching for outstanding applications that fall just beyond established paylines.**

    - Ensure that applications from new investigators have a success rate equal to R01 grants. Such individuals now can be identified on application. The success rate for this group of applicants will be, with exceptions, and estimated 24 percent in Fiscal Year 2000, increasing to 35 to 40 percent in Fiscal Year 2002.

    - Allocate up to 10 percent of competing RPG funds for meritorious applications outside conventional paylines.

    - Continue Accelerated Executive Review (AER) to fund single project applications in patient-oriented and basic research that are near the payline and for which reviewer criticisms can be addressed rapidly. Provide parallel expedited peer-review approaches for Program Project Grants.

4. **Invest in areas that NCI consensus planning processes (e.g., Progress Review Groups, Extraordinary Opportunity Working Groups, Advisory Committees) and staff have identified as presenting special opportunity or need.**

   - Set aside 10 to 15 percent of funds for Requests for Applications (RFAs), Program Announcements (PAs), and applications under other grant mechanisms that target identified gaps and/or emergent opportunities. Monitor investigator-initiated research applications to assess whether these projects alone are meeting programmatic objectives, including those focused on special needs identified in specific disease areas. Use regular, novel, and special award mechanisms to encourage investigation in priority areas. (See sidebar)
     (View an up-to-the-minute listing of initiatives at http://deainfo.nci.nih.gov/funding.htm and http://deainfo.nci.nih.gov/whatsnew/news.htm).

   - Provide sufficient staff, resources, and enhanced electronic communications to improve information dissemination, enhance coordination within and between initiatives, and increase direct contact with applicants and grantees.

5. **Optimize each award to accelerate the pace of discovery.** In Fiscal Year 2000, NCI grant awards averaged four years in duration and were awarded 75 to 90 percent of recommended funds. This level of funding and project duration slows discovery because fewer experiments can be conducted and fewer subjects accrued to clinical trials.

   - Provide funding at full peer-reviewed recommended budget levels for up to five years of support. (To view the current NCI funding allocation levels, visit http://www.nci.nih.gov/admin/fmb/2000Funding.htm).

   - Ensure that investigators have access to NCI-sponsored resources, infrastructure, and technologies that facilitate discovery, both to make progress as quickly as possible, and to create breakthrough opportunities.

   - Triple the amount of funding set aside for administrative supplements to current awardees whose research is going better than expected, or who are poised to test new ideas.

   - Expand R03s, R21, R33, P20 and other award mechanisms that provide seed funds and resources to pilot promising leads.

6. **Facilitate rapid movement from discovery to application by encouraging transdisciplinary and collaborative approaches.**

   - Use established mechanisms and create novel and special mechanisms to encourage collaborative and translational research.

   - Expand administrative supplements to encourage new collaborations that bring together basic and clinical scientists and promote additional interdisciplinary collaborations and

access to central resources such as databases, tissue banks, and animal models. (To access NCI's Research Resources online, visit www.cancer.gov/resources).

- Expand access to resources and technologies that promote interdisciplinary research and collaborations through centers, networks, and consortia.

- Expand cooperative resource programs (e.g., RAID, RAPID, CGAP, EDRN) that give investigators access to technologies and expertise needed to move their discoveries to application.

- Encourage the development of information technology tools to facilitate interdisciplinary communication and collaboration.

- Double the funding for collaborative research awards such as Program Project Grants and cooperative agreement networks in cancer genetics, imaging, early detection, and other areas.

- Expand use of exploratory grants to encourage patient- and population-based research.

Deciding When Unsolicited Ideas Are Not Enough (sidebar)

There are two kinds of investigator-initiated research projects - unsolicited and solicited. Unsolicited projects, freely proposed by investigators, address any research question that is relevant to cancer. The vast majority of the applications received and funded by NCI fall into this category. These projects play a critical role in advancing our ability to prevent and treat cancer. Yet, one may ask how they can help us to develop a well-balanced, coherent research portfolio. They do for a number of reasons. First, there is the significant size of the cancer research community: NCI receives over 8,000 applications each year, covering virtually all areas of relevant science and medicine. Second, identification of critical research needs is far from random. Investigators have easy access to the literature and to the NCI, and their applications reflect the nature of establishments with interests in cancer - medical schools, hospitals, universities, research centers and corporations who focus on this disease. The interests of scientists inherently reflect the goals of their institutions, which are geared to treating cancer and searching for new knowledge relevant to the disease. Third, the system of peer review plays an important role. Success in peer review requires convincing a jury of peers that a project (1) asks an important question, (2) presents a novel and technically advanced approach; and (3) represents an opportunity to advance the state of knowledge. This stringent selection process, along with the other elements discussed above, generally yields a well balanced portfolio.

However, NCI's ongoing planning and evaluation processes sometimes identify imbalances, gaps or opportunities in the research. The Institute then creates incentives to pursue certain research questions through set asides in Requests for Applications (RFAs) and Program Announcements (PAs). These competitions are intended to foster collaborations and channel funds into selected areas of study. We announce funding set asides to assure investigators that,

even though the research problem may seem intractable, or may not have previously fared well in peer review precisely because progress has been so difficult to achieve, that we will commit support for the research area. Often, such competitions help form a critical mass of investigators in a field, which might be further enhanced through use of the cooperative agreement mechanism that provides for NCI coordination and facilitates collaboration across institutional boundaries.

RFAs and PAs also are used to jump start new initiatives, such as those used to implement the "Extraordinary Opportunities" outlined in this document. Judicious use of such competitions can cut years off the time needed to develop a critical mass of research in an emergent field.

CENTERS, NETWORKS, AND CONSORTIA

The Challenge

NCI's mission to translate scientific knowledge into more effective interventions to cure and control cancer is challenged by the conventional ways research is conducted. Basic scientists, clinical scientists, population scientists, and behavioral scientists develop their skills in distinctly different ways and in varied environments with far too little emphasis, except in very select environments, on communicating and working with each other. However, the rapid pace of scientific and technological discovery is creating enormous opportunities that require the close interaction and collaboration of clinical and laboratory scientists from across the research community. The challenge for NCI is to create integrated research environments that foster the complex multidisciplinary interactions needed to address the "big picture" problems in cancer research.

These integrated research environments must functionally link basic, clinical, population, and behavioral scientists to each other and to newly developing diverse fields of science and technology. These scientists must have easy access to many different patients and at-risk populations, tissue banks, new technologies, and state-of-the-art informatics. They must be able to work together with the same ease and flexibility in multi-institutional research settings as in the same institution.

To meet this challenge, NCI continues to create and nurture a new overarching structure for research composed of NCI-designated Cancer Centers, Centers of Research Excellence, networks, and consortia. These infrastructures will enhance the traditional research enterprise in ways that promote and facilitate complex scientific interactions, provide the critical resources essential for the research, and encourage the easy exchange of information and ideas through new communications linkages.

NCI-Designated Cancer Centers

NCI-designated Cancer Centers organize and integrate multidisciplinary research across all departments and schools within a single institution. Having changed the culture of cancer research over the past ten years, the Cancer Centers are engines of discovery that bring the benefits of research directly to the public, providing scientists access to the most advanced technologies and new research opportunities. They link state-of-the art research and clinical care activities within the institution and form key partnerships with industrial, community, and state health organizations outside of the institution. For example, the disease-specific Specialized Programs of Research Excellence (SPOREs), designed to move discoveries from the laboratory into patient and population research settings, had their origins in Cancer Centers. The new Special Populations Network for Cancer Awareness and Research Training (SPN, discussed in the Health Disparities Challenge) is designed to link local, community and regional problems of cancer in underserved populations to the broad-based research capabilities of NCI-designated Cancer Centers. Centers are critical in a new NCI initiative to incorporate Minority Serving Institutions (MSIs) into the NCI's cancer research, education, training, and outreach activities.

The Cancer Genetics Network (CGN) sites are headquartered in Centers. Nearly all of the participants in the Mouse Models of Human Cancer Consortium (MMHCC) are in NCI-designated Cancer Centers. Centers have worked closely with industry in the development of new cancer therapeutic agents and are rapidly becoming significant partners with industry for new technology development.

NCI will create Regional Enhancement Centers to facilitate partnerships between smaller institutions in the country and the large, existing NCI-designated Comprehensive Cancer Centers. These partnerships will provide patients and populations with much improved access to the newest clinical, prevention, and control trials in early detection, prevention, and therapeutic research. NCI anticipates that the Centers will serve another critical function in integrating and coordinating NCI-supported Centers of Excellence, networks and consortia into one overarching, unified research framework and infrastructure.

Centers of Research Excellence

Centers of Excellence (COEs) are composed of interdisciplinary and translational research teams focused on a specific disease, modality, biologic process, or scientific area of particular interest. They are awarded sizeable amounts of flexible funding to enable them to rapidly address emerging scientific opportunities. The first COEs, the SPOREs, were created in 1992 and focused on specific cancers. They serve as translational research engines that move discoveries back and forth among laboratory, clinic, and population research settings. The success of breast, prostate, lung, and gastrointestinal cancer SPOREs has prompted an expansion of the program to other cancer sites, including new SPOREs in ovarian cancer and plans for SPOREs in skin, brain, and head and neck cancers. SPOREs have proven that the NCI can change the culture of the research community into one that is more interactive, more interdisciplinary, and capable of conducting innovative multi-institutional studies.

The SPOREs blueprint has been used in establishing similar COEs in other extraordinary opportunity research areas including, Transdisciplinary Tobacco Use Research Centers, *In vivo* Cellular and Molecular Imaging Centers, and Interdisciplinary Research Teams for Molecular Target Assessment. All of these COEs support interactive, highly multidisciplinary research and provide resources, flexible exploratory funds, and training and career development. NCI will also collaborate with the new NIH Center for Complementary and Alternative Medicine in establishing COEs.

Networks and Consortia

Networks and consortia link the expertise and innovation of scientists from different disciplines and diverse research backgrounds to address important questions and issues about cancer. The CGN addresses the issue of inherited predisposition to cancer and is linking its goals and objectives to those of SPOREs and NCI-designated Cancer Centers. The newly established MMHCC will work closely with SPOREs to develop mouse models that reflect various precancerous and cancerous stages of human cancer. The Diagnostic Imaging Network, a multi-institutional team of scientists, is evaluating and developing a new generation of imaging concepts and tools with device manufacturers and other technology developers. The Early

Detection Research Network facilitates the discovery, development, and validation of molecular markers and assays that detect early signs of cancer and is already interacting with SPOREs and other interdisciplinary teams of scientists. The SPN will involve underrepresented racial, ethnic, and minority communities in establishing research priorities and conducting research that will benefit their populations. NCI-designated Cancer Centers are already linked to the SPN and Minority Institution/Cancer Center Partnerships will link the research-capabilities of NCI Cancer Centers with MSIs. The objectives of the MSI partnership are to train more minority scientists, increase the research capability of MSIs, and improve the effectiveness of Cancer Center research and outreach programs designed to address disparities in cancer incidence and mortality in minority communities.

Networks and consortia interact with NCI-designated Cancer Centers and COEs in a seamless way to advance our understanding of cancer and to improve the prevention, early detection, diagnosis, and treatment of cancer. NCI staff will actively coordinate and link these different research teams, and work with investigators to create a system for communicating across centers, COEs, networks and consortia.

Goal

Create and sustain research infrastructures for collaboration, technology support and development, and access to resources that enable multiple scientific disciplines to address large problems in cancer that could not be solved by individual investigators.

Progress Toward Meeting the Challenge

In the past year, NCI has made considerable progress in completing the foundation for key overarching research frameworks that will bring diverse scientific disciplines together across institutional boundaries. Refining old frameworks such as Cancer Centers and creating new frameworks in the form of COEs, networks, and consortia sets the stage for discoveries that will take maximum advantage of the newest technologies; promote and facilitate a higher order of multidisciplinary, collaborative research; and accelerate improvements in curing and controlling cancer.

NCI-designated Cancer Centers continue to evolve as key strategic partners of NCI. Expansion of the Cancer Centers program continues at a steady pace. In 2000 NCI added a Center in the state of Iowa and will fund a new planning grant for developing a Center in New Mexico. We expect to see another new Cancer Center emerge in the Midwest next year. NCI has been working with institutions in the states of Georgia, New York, Louisiana, Rhode Island, Florida, West Virginia, Kentucky, Arkansas, South Carolina, and Michigan to develop Cancer Centers or become **Regional Enhancement Cancer Centers**. These Regional Enhancement Centers will partner with **NCI-designated Comprehensive Cancer Centers** to improve access. The number of Cancer Centers with the "Comprehensive" designation has increased this year to 37. This means that the capabilities of NCI Cancer Centers to conduct research in the basic, clinical, and population sciences and to conduct education, information, and outreach programs for their communities has increased dramatically. The geographic influence of Cancer Centers continues to expand and has the potential to truly encompass every eligible institution in the Nation.

Specialized Programs of Research Excellence (SPOREs) were established eight years ago to serve as translational research engines focused on specific cancer sites. Sixteen of the 18 SPOREs currently funded are in institutions that house NCI Cancer Centers. In 2000, the SPORE program added a new cancer site and funded four ovarian cancer SPOREs. These research teams already are establishing research links and preparing to conduct inter-institutional research that cannot be accomplished through any other venue. In addition, the SPORE program has become open to all types of cancer through a transition plan that will gradually add new cancers over the next five years. Our goal is to have a system in place for the sixth year that will allow any new cancer site research group to submit an application for competitive support once a year.

NCI recently launched the **Minority Institution/Cancer Center Partnerships (MICCPs)** to engage minority institutions in NCI's research activities, including training, education, and community outreach. It will engage the five major institutions with medical schools (Drew, Meharry, Howard, Morehouse, and Puerto Rico) and also will provide opportunities for over 300 other smaller institutions throughout the Nation to partner with NCI-designated Cancer Centers and contribute to the mission of NCI.

The Plan

Our goal applies to all NCI-designated Cancer Centers, networks and consortia, but this plan focuses primarily on the objectives and resources for the Centers and SPOREs. Many networks and consortia activities are budgeted in other Opportunities and Challenges throughout this document. For a complete list of centers, networks, and consortia discussed in this document, see the sidebar on page x.

Objectives and Milestones for Fiscal Year 2002

1. **Increase the number and broaden the geographic distribution of NCI-designated Cancer Centers.**

   - Designate 2 new Cancer Centers.
   - Award 2 new Cancer Center Planning Grants.
   - Establish 3 Regional Enhancement Cancer Centers that collaborate with NCI-designated Comprehensive Cancer Centers to expand the base of patients and populations available for early detection, prevention, and therapeutic research studies.

- Award 5 Cancer Center Supplements to encourage inter-center research collaborations when patient, community, and regional responsibilities are in competition or when combining resources can address important questions more effectively.

- Establish formal affiliations between Cancer Centers and Minority Serving Institutions (MSIs) in the form of 2 comprehensive partnerships, one planning grant for a comprehensive partnership, and 10 planning grants to increase the number of minorities engaged in cancer research, enhance research capabilities of MSIs, and improve the effectiveness of Cancer Centers in serving minority communities. (See Objective 4, Education, Training, and Career Development Challenge for the training component of these partnerships.)

2. **Expand the capacity of Cancer Centers to engage in newly developing areas of research and technology and to act as platforms for translating discoveries into interventions.**

    - Establish 10 Advanced Technology Programs in Cancer Centers to enable work with industry to develop, access, and export the newest technologies for solving important problems in cancer research.

    - Increase funding to all Cancer Centers to encourage scientists in Centers to develop new technologies and methodologies for entirely new approaches to answering important cancer research questions.

    - Establish 10 Informatics Planning Activities in Cancer Centers to build critical informatics capabilities of data acquisition, analysis, integration, and coordination in partnership with the NCI.

    - Provide additional funding to build the clinical research and population research infrastructure of Cancer Centers. Fund databases that conform to NCI's clinical informatics infrastructure, support population studies, and provide more core staff to conduct innovative translational therapeutic and prevention trials.

3. **Expand and enhance the research of Specialized Programs of Research Excellence (SPOREs).**

    - Expand the scope of the SPORE program to include the following additional SPOREs: 2 in breast cancer, 2 in prostate cancer, one in lung cancer, 2 in ovarian cancer. Add the following SPOREs: 2 in head and neck cancer, one in genitourinary tract cancers, one in skin cancer and 2 in brain cancer. Continue to implement the transition plan to include all cancer sites by Fiscal Year 2005.

- Provide supplements to SPOREs for planning and developing complex inter-SPORE research projects and for collaborative projects with other NCI COEs, networks, and consortia.

- Support the development of an Internet platform and research database to enable SPOREs to exchange research results and to foster communications for sharing resources and developing collaborative inter-SPORE research projects.

4. **Develop a system for linking and managing the entire research framework of centers, COEs, consortia, and networks.**

   - Create a flexible management system for planning, initiating and completing complex collaborative research projects among centers, COEs, consortia, and networks that provides for specialized short-term resources and research support.

   - Develop a communications network that enables centers, COEs, consortia and networks to identify areas of common interest, share research information and resources, develop a continuing research dialogue, and identify areas of potential collaboration.

NCI Centers, Networks, and Consortia Referenced in This Document

Centers	Section/Page
NCI Cancer Centers	Centers Challenge p.
Biology-Chemistry Centers	Molecular Targets Opportunity p.
In Vivo Cellular and Molecular Imaging Centers	Imaging Opportunity p.
Minority Institution/Cancer Center Partnerships	Centers Challenge p. and Training Challenge p.
Small Animal Imaging Resource Program Centers	Imaging Opportunity p.
Specialized Programs of Research Excellence (SPORES)	Centers Challenge p.
Transdisciplinary Tobacco Use Research Centers	Tobacco Opportunity p.
Centers of Excellence in Cancer Communications	Cancer Communications Opportunity p.
Centers for Population Health	Health Disparities Challenge p.
Advanced Technology Center	Signatures Opportunity p.

Networks and Consortia	
Diagnostic Imaging Network (also known as American College of Radiology Imaging Network)	Imaging Opportunity p.
Cancer Intervention and Surveillance Modeling Network	Trends Challenge p.
Breast Cancer Surveillance Consortium	Trends Challenge p.
HMO Cancer Research Network	
Cancer Genetics Network	Genes and the Environment Opportunity p
Early Detection Research Network (EDRN)	Signatures Opportunity p.
Tissue Networks Cooperative Breast Cancer Tissue Resource Cooperative Human Tissue Network Cooperative Prostate Cancer Tissue Resource	Signatures Opportunity p.
Interdisciplinary Research Teams for Molecular Target Assessment	Molecular Targets Opportunity p.
Director's Challenge (10 Consortia involving 24 Institutions)	Signatures Opportunity p.
Mouse Models of Human Cancer Consortium (MMHCC)	Genes and the Environment Opportunity p and Signatures Opportunity p.
Special Populations Networks for Cancer Awareness, Research, and Training	Health Disparities Challenge p.
NEMA/FDA Partnership	Imaging Opportunity p.
Interagency Council on Biomedical Imaging in Oncology	Imaging Opportunity p.
Cohort Studies Consortium	Genes and the Environment Opportunity p.
Shared Pathology Informatics Network	Signatures Opportunity p.
NASA/NCI Biotechnology Forum	Signatures Opportunity p.
National Cooperative Drug Discovery Groups (NCDDG)	Molecular Targets of Prevention and Treatment Opportunity p.

NATIONAL CLINICAL TRIALS PROGRAM

The Challenge

The research investment of the past decade has produced major advances in our understanding of tumor biology and molecular targets – the tumor-related molecules that can be selectively targeted to treat or prevent cancer. It also has brought about a dramatic increase in the number of new preventive, diagnostic, and therapeutic agents being tested in clinical trials. But our present clinical trials system is failing to keep pace with the growing number of agents that will merit testing in people. During the 1990s the number of new cancer treatments in development by industry increased threefold to over 350. In 2000, NCI began clinical trials on about 30 novel agents discovered through its own drug discovery programs or in collaboration with academic institutions or industry. This is in addition to 78 promising new interventions for treatment and 32 for prevention that NCI already is testing in people.

As these potential treatments and prevention strategies emerge from early clinical testing, NCI is faced with a backlog of agents that need to enter large Phase III trials – the final crucial step in the translation of new discoveries into effective new treatments and prevention strategies for patients. At present, NCI and its grantees are able to initiate only about 30 Phase III trials each year. Compounding this problem is the fact that for a variety of reasons – including limited access, lack of insurance coverage, patient-physician communication issues, and therapy choice – only about 20,000 patients enter Phase III trials each year. Overall, fewer than three percent of patients with cancer participate in the clinical trials that define effective new treatment approaches. Thus, it can take over four years just to recruit enough patients for the average Phase III trial. In addition, more than 80 Phase II and III prevention trials have been initiated, but progress in this area is limited by lack of methods, such as biomarkers, to determine the effect of a preventive over a short period of time, lack of technologies to improve precision in characterizing precancerous lesions, and the growing number and complexity of trials needed to determine the roles of this new generation of agents.

How can we more efficiently convert recent scientific discoveries into effective interventions, eliminate the backlog of agents for testing, and increase patient access? We must invest in, restructure, and increase the capacity of our national clinical trials program. Within the past three years, NCI has reconfigured major aspects of its clinical trials program to increase the speed and smooth the path for entering promising agents into trials. While the time from initiation of clinical trials to Food and Drug Administration (FDA) approval has improved over the past decade, the clinical development required to establish the best uses of new agents still occurs over a much longer period. For example, paclitaxel (Taxol®), approved for use in ovarian cancer in 1992, also has a potentially life-saving role in several other cancers, including cancers of the breast, lung, prostate, head and neck, esophagus, and bladder. Even so, the clinical trials to define its use in these diseases are still ongoing several years after FDA approval for ovarian cancer treatment.

The changes we propose in the following plan will substantially increase the number of trials and number of patients who enroll in trials each year by easing the way for physicians to

communicate with patients and enroll them in clinical trials. The plan also calls for funding the kinds of laboratory studies that will help determine why particular drugs are effective in some patients and not in others. The results will help us tailor treatments for cancer patients in the future. These enhancements will help speed development of new agents and alleviate the backlog of agents awaiting evaluation.

Goal

Ensure that the Nation's cancer clinical trials program is poised to address the most important medical and scientific questions in cancer treatment and prevention quickly and effectively through state-of-the-art clinical trials that are broadly accessible to cancer patients, populations at risk for cancer, and the physicians who care for them.

Progress Toward Meeting the Challenge

NCI is revitalizing its clinical trials system to accelerate the pace of clinical research by finding new and better ways to generate ideas, broaden access for physicians and patients, educate and communicate, streamline procedures, and automate data systems. NCI is committed to increasing funding for our clinical trials Cooperative Groups, through which most patients enter trials (See p. x for more Cooperative Groups information.) Group funding has increased over 50 percent since 1999.

Generating New Ideas

NCI's new clinical trials system provides avenues to enable research ideas from all groups with an investment in clinical trials to be collected and considered. New forums and review processes allow wider collaborations and provide streamlined approval for the most promising clinical trials concepts.

- **State of the Science Meetings** are national forums that identify disease-specific research gaps and opportunities in order to advance important scientific findings into definitive clinical evaluation as quickly as possible. These meetings also stimulate new opportunities for integrated translational research with a focus on diagnostic, preventive and therapeutic findings.

- **Concept Evaluation Panels** composed of NCI staff and external experts are being tested in the evaluation of Phase III clinical trial proposals for treatment of genitourinary and lung cancers.

- **Quick-Trials** provide investigators with rapid access to support for pilot, Phase I, and Phase II cancer clinical trials testing new agents and patient monitoring, and laboratory studies for development of new therapeutic approaches. Originally piloted in prostate cancer, the program now is being expanded to all cancer sites.

- The **Clinical Oncology Special Emphasis Panel** provides the clinical oncology community with its own NIH study section. Phase I, II, and III clinical trials in prevention and treatment can be reviewed as can translational research linked to a clinical trial.

- **Clinical correlative science studies** are being funded to deepen our understanding of the relationship between tumor characteristics and patient outcomes.

Broadening Access

It can sometimes take years to complete patient accrual for large Phase III trials despite the fact that studies have shown that costs for patients on clinical trials are comparable to those receiving standard treatment. The new clinical trials system is designed to speed completion of studies and increase access for both physicians and patients.

- The **Expanded Participation Project** (EPP) extends access to NCI-sponsored Cooperative Group studies for qualified oncologists who are not Group members to the Groups' menus of studies.

- **Special Populations Networks for Cancer Awareness, Research and Training** support minority enrollment in clinical trials by fostering awareness and building relationships between research institutions and community-based programs. Ongoing NCI efforts have raised the proportion of minority participation in treatment trials to nearly 20 percent.

- A **Physician Communication Module** provides Howard University Cancer Center physicians who are interested in participating in NCI clinical trials with the technology to easily enroll patients and follow them on clinical treatment protocols.

- NCI's **payer and provider partnerships** with the Department of Defense TRICARE/ CHAMPUS health care system and the Department of Veterans Affairs provide coverage for clinical trial participation for military personnel and veterans. An agreement with the United Health Care Corporation and the Coalition of National Cancer Cooperative Groups, Inc. covers costs for medical care in multi-institutional clinical trials.

Educating and Communicating

Before participating in clinical trials, it is critical that patients and physicians understand the value of clinical trials and are able to access the system. NCI is developing an extensive set of communication programs to deliver tailored clinical trials information to physicians and patients.

- **cancerTrials** (cancertrials.nci.nih.gov) is NCI's online gateway to clinical trials resources. It integrates information about clinical trials participation, trials results, and related resources for patients and physicians.

- **CancerNet**, accessible through cancerTrials, hosts NCI's searchable clinical trials database with over 1,800 active clinical trials and an archive of over 11,000 closed trials.

- The **Cancer Clinical Trials Education Program** trains nurses and social workers to educate patients and their families about clinical trials. NCI also is partnering with professional societies and health plan organizations to develop Web-based and self-paced modules about clinical trials participation for physicians and nurses.

- The **Cancer Trials . . . Because Lives Depend On It** project is testing a new approach to clinical trials accrual. Partner organizations recruit "campaign ambassadors" who attend training programs and encourage their communities to consider participating in trials.

- New **Minority Clinical Oncology Awards** provide underrepresented minority health professionals recently trained in the clinic with the opportunity to gain the biomedical research expertise necessary to become clinical oncologists. They also support researchers committed to oncology for underserved minority populations or field-based research.

Streamlining Procedures

In addition to improving research quality, the new clinical trials system will provide tools that reduce the time it takes to create protocols, have them reviewed, and enroll patients.

- The **Cancer Trials Support Unit** (CTSU) streamlines and centralizes administrative, financial, and data collection tasks associated with clinical trials. It provides participants access to NCI's entire Phase III clinical trials system.

- A team representing the breadth of the cancer community created an **informed consent** template and recommendations to improve patients' understanding of cancer clinical trial participation.

- A **Central Institutional Review Board** (IRB) including advocates, ethicists, and oncology professionals was established for multi-center trials. This new NCI and NIH Office for Protection from Research Risk model reduces the number of local IRBs that must review and approve the same protocol.

- **Protocol assembly**, the submission and development of ideas for protocols, is easier because NCI has created a series of electronic forms, templates, and databases that eliminate paperwork, aid in tracking trials information, and streamline review.

- **Clinical Trials Monitoring Branch (CTMB) Audit Information System** is a Web-based information system that permits online submission of all data collected during quality assurance audits of NCI-sponsored Cooperative Group clinical trials.

Automating Data Systems

NCI is constructing a clinical trials informatics system with several interlinked components that reduce paperwork, standardize language, and speed the reporting of clinical trials data.

- The **Common Toxicity Criteria** is a standard language for reporting adverse events occurring in cancer clinical trials.

- The **Adverse Event Expedited Reporting System** is a Web-based system for reporting to NCI serious or unexpected events that occurred on trials of NCI-sponsored agents.

- The **Clinical Data Update System**, NCI's primary data reporting mechanism for clinical trials, standardizes **and** streamlines data reporting and reduces administration.

- **Common Data Elements** (CDE), terms that medical providers may use to collect and report patient information for clinical trials, have been developed by NCI and its partners The CDE promotes a common vocabulary among cancer research organizations.

The Plan

Objectives and Milestones for Fiscal Year 2002

1. **Identify and address compelling clinical questions confronting patients struggling with cancer and their physicians.** We will identify the most promising scientific leads for clinical evaluation and optimize use of existing clinical trials infrastructure to address a broader array of approaches to reducing the burden of cancer.

    - Conduct disease-specific State of the Science meetings semi-annually in gastrointestinal, lung, genitourinary, and prostate cancers, and leukemia to identify important research questions and define a scientific research agenda to address them

    - Expand Concept Evaluation Panels beyond initial lung and genitourinary cancer pilots to provide rigorous peer review of all concepts for Phase III trials sponsored by NCI.

    - Provide scientific leadership funds to researchers who chair studies and statisticians responsible for writing, monitoring, and analyzing NCI-sponsored, high-priority Phase III trials.

- Provide translational research funds for clinical correlative studies to uncover the mechanisms of action, response, and resistance underlying new treatments and preventive strategies, and to translate basic biology from the bench to the bedside.

- Support a national tissue resource system that includes normal, precancerous, and cancer tissues, to facilitate rapid evaluation of new assays and relevant clinical correlations as new targets are identified. (See Signatures, objective 2, p. x.)

- Fund tissue banks to store tissues from cancer patients undergoing treatment to allow later studies of drug effectiveness, molecular abnormalities, and clues to tumor initiation and progression.

- Develop and make widely available through COEs molecular assays required to characterize/classify tumors.

- Integrate treatment and prevention research into the clinical trials infrastructure.

- Incorporate behavioral, epidemiologic, and outcomes research, and other relevant areas to most effectively address the burden of cancer in specific tumor types and patient populations.

- Incorporate the evaluation of relevant biomarkers into clinical trials.

2. **Increase the pace of development and clinical testing of promising new therapeutic and preventive agents.** Over 2-3 years, we will triple the number of promising agents entering NCI sponsored clinical trials, triple annual patient accrual to early clinical trials of promising agents, quadruple accrual to pivotal or proof-of-principle early clinical trials, and double accrual to Phase III clinical trials.

    - Expand resources for the Rapid Access to Intervention Development and Rapid Access to Prevention Intervention Development programs. (See Targets, objective 2, p. x.)

    - Increase funding for early therapeutics development contracts to fund multi-institutional consortia that are able to accrue many patients rapidly and perform sophisticated correlative laboratory studies.

    - Fund COEs in Interventions Directed to Molecular Targets to develop the necessary assays, tools and approaches to assess the effects of promising new agents on their molecular targets.

- Fund Cooperative Groups and practice sites to support data management and allow physician participation in clinical trials at double to triple the current rate through Cancer Trials Support Units.

- Support rapid grant review process for mechanism-based clinical trials.

3. **Substantially increase the participation in clinical trials of patients, individuals at risk for cancer, and the physicians who care for them.**

   - Use the Expanded Participation Project to fund new participating physicians, including new minority physicians, to hire the necessary research nurses and data managers for effective participation.

   - Expand CTSUs to consolidate all administrative tasks associated with clinical trials for greater efficiency and ease of use.

   - Provide extensive information about treatment and prevention options and clinical trials to enable patients and physicians to make informed medical choices. (See Informatics, p. x.)

   - Develop uniform data reporting mechanisms and informatics support to facilitate clinical trials participation. (See Informatics, p. x.)

4. **Reduce outcome disparities in special populations by increasing access to state-of-the-art clinical trials in cancer treatment and prevention.**

   - Create a Clinical Trials Outreach Program to increase participation by underrepresented populations; establish clinical trials units at historically black medical institutions; strengthen clinical trials units at minority-based community oncology sites.

   - Increase clinical trials participation by minority physicians and health professionals by implementing an NCI fellowship training program in clinical trials for minority physicians and forums for minority scientists' input into developing clinical trials that address issues of special importance for minority and special populations.

INFORMATICS AND INFORMATION FLOW

The Challenge

Around the globe, patients and cancer researchers alike are benefiting from the explosive growth of the World Wide Web and advances in computing. But vast amounts of existing knowledge often go unused due to an inability to access and organize material from diverse sources. Therefore, we must ask ourselves, "How do we best collect, manage, and share this information?" The answer to this question lies in designing a standards-based framework and a set of tools that will enable us to capture, analyze, apply, and reuse knowledge. This framework and related tools will create interfaces among the research communities – basic, translational, clinical, and population-based – that participate in the discovery process *and* with consumers and individuals who deliver cancer care and/or require information.

NCI is developing a knowledge management framework that will unify the research and cancer practice communities. Easy access to cancer knowledge will reduce drastically the time and effort needed to create and use existing or new information. Cancer research and care will be transformed by the effective and efficient information exchanges among all involved in cancer research and by the rapid translation of research observations into clinical interventions. A common knowledge management framework will create new synergies within and among the fields of research described in this document, resulting in a dramatic acceleration of our progress against cancer.

The first steps being taken are to use the common knowledge management framework to increase the speed with which we carry out clinical trials in cancer prevention, diagnosis, and treatment. We have revised our criteria and standards for reporting all data collected during a clinical trial, and are developing common forms, terminology, and reporting requirements across all types of clinical trials. This uniformity will increase the speed, efficiency, and accuracy of results reporting. Special databases of medical and scientific terminology will help researchers, clinicians, and other users of NCI information systems to find and understand the information they seek. NCI's leadership in this area will enable us to establish a national clinical trials effort that realizes maximum benefit from the information revolution through increased patient accrual, common reporting practices, and greater sharing of knowledge with the public and the research community. This effort is complemented by NCI efforts to provide informatics integration of the research programs outlined in its areas of Extraordinary Opportunity. An extension of the informatics efforts deployed to support the NCI's Cancer Genome Anatomy Project (CGAP), this program will overcome the traditional barriers that block communication of research information between differing scientific disciplines. The NCI informatics infrastructure will help us address the issue of compatibility, enable us to manage the explosive growth in fundamental discoveries, and help alleviate the serious bottleneck that exists between discovery and its application for the benefit of patients with cancer. By moving quickly to implement the framework and to develop general tools, we can speed discovery, lower costs for all participants, and capture data electronically in a way that makes information accessible to all participants in the cancer community.

Goal

Create a Cancer Informatics Infrastructure (CII) that enables cancer research by enhancing information and resource exchange among researchers, clinicians, and the public and reduces the barriers experienced by individuals seeking information about cancer prevention, diagnosis, and treatment.

Progress Toward Meeting the Challenge

During the past year, NCI designed, launched, or enhanced several components of the Cancer Informatics Infrastructure (CII), a unified, multifaceted and versatile knowledge management system. Our progress on this and related projects is described below.

- Scientists participating in clinical trials often are burdened with large amounts of time-consuming paperwork that has become integral to the clinical trials' operation. To reduce this burden for participating researchers and help them more efficiently develop protocols and test advances in clinical oncology, NCI is creating the **Clinical Trials Informatics System**. This innovative system links all phases of the clinical trial life cycle, from protocol development, distribution of information to assist patient recruitment, screening, and protocol implementation to publication of clinical trials results. Several computer-based components of the system were launched in Fiscal Year 2000, including the **Protocol Authorization and Tracking System (PATS)**, the **Drug Authorization and Tracking System (DARTS)**, the **Clinical Data Update System (CDUS),** the **Clinical Trials Support Unit (CTSU),** and a **Web-based clinical trials prototype for electronic submission of clinical trials to PDQ/CancerNet**. PATS is a document management tool designed to streamline the collection of clinical trials' data that is relevant to the scientific, regulatory, administrative, and communication needs of the Institute. This tool will help to automate the protocol development process, allowing investigators and NCI staff to concentrate on scientific issues rather than on administrative details. It also will provide administrative information for updating and maintaining NCI's clinical trials registry available through the CancerNet Web site. DARTS – a real time drug inventory developed to reduce drug wastage and to support the scientific and safety evaluation of new treatment agents – has been developed to efficiently automate the procurement and distribution of agents used in clinical trials. CDUS, the primary clinical data reporting mechanism for NCI-sponsored trials, will help to standardize and streamline clinical data reporting to NCI in the simplest and most efficient manner possible in an effort to facilitate drug development and clinical research. The CTSU will offer oncologists a large portfolio of clinical trials and easy-to-use Web-based patient and enrollment data forms. The CTSU system is being developed using components already in use at NCI, including **common data elements,** the **clinical trial enterprise models,** and the **PDQ/CancerNet clinical trials registry**. In Fiscal Year 2000, we created common data elements for breast, lung, and colon cancer treatment clinical trials to help simplify and standardize data collection. In the coming year, we plan to expand our efforts to include five additional disease sites and prevention, early detection, and screening trials. Continued collaboration among all NCI programs involved in informatics activities

enables us to take full advantage of newly developed systems to enhance existing ones. Finally, **a Web-based clinical trials prototype for electronic submission of clinical trials to PDQ/CancerNet** allows researchers to electronically submit, review, and approve the information put into the PDQ/CancerNet clinical trials registry prior to posting. It also will be used to electronically update information on clinical trials as protocols are amended or as participating investigators or study status changes.

- NCI has made substantial progress in creating a new **XML/SGML-based information infrastructure** to support its comprehensive cancer information products and services, including PDQ and CancerNet. A recently developed search and retrieval engine provides the much-improved functionality of the redesigned CancerNet Web site. In addition, work is underway to create a powerful new data repository that will allow construction, integration, and maintenance of comprehensive cancer-related information. This new system will support a broad range of content received from a variety of sources, including multimedia assets.

- NCI is continuing development of **The Science Place** (SP), a knowledge management tool created to enable scientists, analysts, and managers to search and retrieve information from many sources, to organize and interrelate it to reflect their personal interests, and to share their information with others. The SP, launched this year after several years of development, enables users to automatically analyze Web-based and other documents for information of interest based on semantic mappings from online vocabulary systems. It also serves as a portal to other NCI tools, such as the Grant Retrieval Information Technology System.

- To fully understand the needs of the cancer research community across the many forms of cancer, an accepted system of categorizing science is needed. Similarly, a commonly agreed upon system for categorizing research is needed to help NCI communicate its activities to its many constituents. Responding to this need, NCI developed the **Cancer Scientific Outline** (CSO), a simply designed tool that enables us to categorize our research in a scientific and disease-related manner. By providing the means to create a national/international research portfolio, the CSO can have a profound effect on shaping cancer related research planning. Using this instrument, NCI and its fellow cancer research funding agencies will have a greater opportunity for enhanced communication and a foundation for informed discussions and planning. To date, NCI has coded into the CSO extramural grants and contracts from FY1997 through FY1999. In addition, NCI worked over the past year with the Department of Defense (DoD) U.S. Army Congressionally Directed Medical Research Program to begin coding into the CSO the program's significant research portfolio in prostate, breast, and ovarian cancer. NCI's intramural projects will be coded next. In the near future, NCI and DoD plan to expand the CSO project, inviting six cancer funding organizations to join in creating a national/international cancer-related research portfolio. Plans also are underway to make the CSO-coded research portfolio available to the public in a Web friendly and searchable format.

- Often, cancer researchers are not aware of the many scientific tools and research resources that NCI has developed or supported to facilitate rapid progress in this field. To inform researchers about these many tools and resources, NCI has developed a Web-based directory known as **NCI Research Resources**. This award-winning database directs researchers to resources that are generally accessible without extensive negotiation or intellectual property issues. This catalog, which includes descriptions of each resource as well as contact information, can be accessed online at http://cancer.gov/resources.

- Using the rich and diverse collection of data generated through the various components of the Cancer Genome Anatomy Project (CGAP), NCI has created an **integrated model of cancer-related genomic data and developed a portal that provides a cancer researcher-oriented view of CGAP generated data**. This portal permits researchers to "mine" information such as gene expression patterns in different tissue types and data or gene variants in the population.

- NCI has developed and implemented a **modular, scalable architecture that facilitates the rapid development, deployment, integration, and maintenance of NCI Initiative-specific World Wide Web sites**. This architecture has been used to deploy the prototype Web sites for the CGAP portal, the Mouse Models of Human Cancer Consortium, and the Director's Challenge. In support of the CGAP Web portal, NCI also has developed a prototype for an open source-based informatics architecture that facilitates the retrieval and integration of data distributed among multiple, independent data sources.

The Plan

Objectives and Milestones for Fiscal Year 2002

1. Expand the NCI's informatics infrastructure to enable integration and interface within and among basic, clinical, translational, and population research initiatives.

- Establish a Center for Bioinformatics that supports the integration of data and tools generated through the NCI's Extraordinary Opportunities and facilitates information exchange within and between NCI supported research initiatives.

- Establish a toolbox of open source informatics applications and services based on a common set of operating principals and standards that support diverse cancer research activities.

- Develop research tools that exploit and institutionalize the use of common data elements and a common vocabulary to further the exchange of all types of cancer information and data among the cancer community.

- Create a standing review panel for NCI information standards that formalizes NCI's role in the national standards development process and incorporates these standards into the development of global informatics research tools.

2. **Make information on cancer research, diagnosis, treatment, screening, and prevention more readily accessible to the entire cancer community, including physicians, patients, survivors, family members, and persons at risk.**

   - Equip the NCI's cancer information system with powerful facilities for creating, integrating, and accessing a wide range of cancer information resources, including richly formatted and modular text documents and multimedia assets such as images, sound, and video. This technical infrastructure is essential to improving access to relevant and easily understandable cancer information.

   - Take full advantage of the NCI's restructured cancer information system to enable all types of users to precisely and easily identify and interpret information relevant to their concerns. This technology will enable users to move seamlessly between different layers of information so they can find the level most appropriate to their needs. Accomplishing this will require restructuring and indexing of current NCI products, including the approximately 300 cancer information summaries and the 1,800 ongoing clinical trials descriptions in CancerNet/PDQ. Once complete, users will be able to identify clinical trials based on specific eligibility criteria.

   - Develop Web-based search tools and user interfaces to extend the NCI's comprehensive electronic cancer information system, making research results and clinical trials information more easily accessible to the public. Extensive cancer vocabulary support will enable creation of both simple and expert search options, including interactive interfaces that guide users to information specific to their needs.

   - Perform ongoing evaluation of the feasibility of using concept-based searching and natural language processing. Pilot tests will be performed on existing NCI cancer information systems such as PDQ/CancerNet to ensure that as the technology advances NCI is positioned to take advantage of the value these techniques offer.

   - Develop an outreach plan that encourages voluntary electronic submission to PDQ/CancerNet of information about non-NCI sponsored clinical trials, such as trials conducted by pharmaceutical companies and European clinical trials organizations.

   - Modify the processes for writing and reviewing all clinical trials so that

development and review can be completed in less than three months. Develop an outreach plan that informs and encourages the voluntary electronic submission of information on non-NCI sponsored clinical trials to PDQ.

3. **Make informatics tools easily accessible and use them to integrate and disseminate information from different cancer research communities.**

   - Expand the capacity to maintain and distribute an inventory of tools and technologies developed through the NCI.

   - Develop an easily accessible and comprehensive electronic clinical trials system to provide uniform and easy access, enhance clinical trials recruitment, and promote scientific knowledge exchange among all participants.

   - Further develop information portals such as the Science Place and the CGAP Web site as broad information access points that provide scientific and clinical information to the research community.

   - Expand systems and tools that facilitate the grant/contract review and award process and simplify management of NCI's cancer research portfolio.

   - Develop and provide methods for non-NCI Web sites and information services to directly search and retrieve information from the NCI's comprehensive cancer information system.

STUDYING EMERGING TRENDS IN CANCER

The Challenge

Identifying and tracking rates and trends in our national cancer burden, and monitoring the factors that influence these changes are a crucial underpinning of efforts to prevent and control cancer. We are making real progress against cancer, and reduction in the cancer burden on people is a critical measure of that progress. Between 1990 and 1997, new cancer cases and death rates dropped for all cancers combined and for most of the top ten cancer sites, reversing a decades-long trend of rising rates in cancer incidence and death in the United States. These decreases are hard evidence of the wisdom of this Nation's investment in cancer research.

Appropriate decision making in science and in public health depends on accurate, reliable information about the incidence and impact of disease. Established in 1973, NCI's Surveillance, Epidemiology, and End Results (SEER) cancer registry program has been a world model for tracking population trends in cancer morbidity, survival, and mortality. The NCI cancer surveillance program uses SEER data to identify and study variations in cancer rates, assess trends, track the impact of cancer on the general population, and provide information that researchers need to ask critical questions about why certain populations are affected by cancer more severely than others. SEER data have enabled us to identify environmental carcinogens, monitor cancer-related effects of tobacco on men and women, identify geographic areas with higher than average cancer rates, study patterns and outcomes of cancer care, and identify risk groups for research and public health intervention programs.

Recent changes in health care financing and delivery, the revolution in informatics and computer programming technology, and the social and cultural diversity of our country present new challenges and opportunities in surveillance research. Currently, our understanding about how risk factors, screening, and treatment may affect trends in the cancer burden is beginning to unfold, and advancing knowledge in these areas will require new data sources and statistical methods. To more fully assess the Nation's cancer burden, we need data on patterns of care and patient-centered measures, such as quality of life and sociodemographic and economic population characteristics, in addition to the incidence, survival, and mortality data now collected. Research is needed to improve methods for measuring quality of life, quality of care, health status, morbidity, family history, cancer risk behaviors, screening, and treatment as well as methods and models for relating these measures, quantifying their impact on current and future cancer rates, and predicting outcomes. In addition, new investments are required to support the adoption of methodologic and informatics tools that will improve the precision and expand the reach of our cancer surveillance efforts. These technologies include geographic information systems that allow data linkage and statistical analysis of individuals and potential environmental exposures by location, new approaches to modeling trends, and more refined cancer maps and spatial statistical techniques for assembling, analyzing, and disseminating cancer surveillance data.

NCI's surveillance efforts should be expanded to cover the broad spectrum of the racial, ethnic, socioeconomic, and cultural diversity of our country. New investments in surveillance research

on specific population groups will make it possible to connect information on prevention, risk factors, screening, treatments, and patterns of care with outcomes such as incidence, quality of life, and survival.

Greater efforts are needed to disseminate the results of NCI's surveillance research to the general public policy makers, and advocacy groups. In addition, we must improve our ability to provide epidemiologists and other science based investigators with the information crucial to developing new ideas for research on cancer's causes and for developing interventions based on study findings. As the field of surveillance research expands and takes on these new challenges, it is clear that scientists with skills that encompass the disciplines of epidemiology, statistics, disease registration, geographic information systems, and informatics are in short supply. To strengthen this maturing scientific discipline and ensure that we have the data and data systems we need to guide cancer research activities of all types, we must create the training opportunities necessary to prepare the next generation of surveillance researchers. Finally, enhancing our investment in surveillance research will ensure that NCI continues to play an active and visible national leadership role in developing a comprehensive national surveillance program.

Goal

Expand surveillance data systems, methods, communications, and training to improve capacity for monitoring progress in cancer control and for exploring potential causes of cancer nationally and among diverse populations.

Progress Toward Meeting the Challenge

Through a variety of new initiatives, NCI is expanding surveillance data collection systems and research methods to assess the burden of cancer across all populations. Examples of recent progress in meeting our challenge follow.

Improvements in cancer surveillance have generated mounting interest among health professionals and the general public about factors that contribute to the cancer burden and that can be modified through both individual and societal efforts. To make this information more available to researchers and the public, NCI scientists, working with the editorial staff of the *Journal of the National Cancer Institute* (JNCI), developed the **Cancer Surveillance Series**, consisting of research articles that address emerging patterns of cancer in various population groups in the United States and explore the elements (risk factors, screening, diagnosis, and treatment) affecting these patterns at the national and regional level. The series, begun in June 1999, is providing a forum for disseminating the latest analysis and evaluation of cancer statistics in the United States, with special emphasis on data from population-based cancer registries in our SEER program. Similarly, NCI recently published the **Atlas of Cancer Mortality in the United States, 1950-1994**, showing geographic patterns of cancer death rates in over 3,000 counties across the country. The 254 color-coded maps, which are accessible on the Web (http://www.nci.nih.gov/atlas) make it easy for researchers and state health departments to identify places where high or low rates of cancer occur, and to uncover patterns of cancer that would escape notice if larger areas, such as states, were mapped.

To further understand the burden of cancer among all populations, NCI is **expanding its cancer surveillance program** to cover a broader spectrum of the racial, ethnic, socioeconomic, and cultural diversity of our country, which will in turn improve our ability to describe the cancer burden across a broader spectrum of the population. NCI is expanding SEER (http://www-seer.cancer.gov/) to enhance coverage of rural whites and blacks, non-Mexican Hispanics, American Indians, and states with high cancer death rates. In 1999, coverage of Alaska Natives was added to the SEER Program and development projects were maintained to improve the quality of data on American Indians. **Collaborative studies such as the National Longitudinal Mortality Study involving the NIH, the Census Bureau, and the National Center for Health Statistics** were launched in 1999 to improve cancer mortality data for racial, ethnic, immigrant, and socially disadvantaged populations through funding of data links with the Current Population Surveys, the National Death Index, and the SEER Program. These links will make it possible to connect important socioeconomic and demographic information on cancer rates with prevention, risk factors, screening, treatment and patterns of care for these special populations.

Computer software referred to as **SEER Stat** has been developed and has greatly facilitated access to and analysis of SEER data. This software is provided free of charge on SEER public use files that currently are being distributed upon request at a rate of more than 1,500 per year. This software has been tailored for use by a large number of registries participating in the CDC National Program of Cancer Registries. In addition, a database management system for SEER cancer registries is being developed to more efficiently support registry operations and promote more uniform standards and consistency among U.S. population-based cancer registries.

Enhancing our understanding of trends in cancer involves collecting descriptive information on lifestyle factors and behaviors such as smoking, diet, physical activity, and screening practices and linking this information to cancer outcomes in defined populations. Several initiatives are underway to support collection of risk factor and screening data with cancer outcomes data. A Cancer Control Topical Module is now being fielded in collaboration with the National Center for Heath Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC) as part of the National Health Interview Survey (NHIS). This model provides critical data at the national level to track progress in major cancer control health practices. In a similar effort at the state level, NCI is partnering with the California State Department of Public Health to initiate for the first time in California a state level survey similar to the NHIS, the California Health Interview Survey (http://www-dccps.ims.nci.nih.gov/ARP/RiskFactor//chis.html). Seven new centers and a statistical coordinating center were funded this year to continue the support of the Breast Cancer Surveillance Consortium (BCSC) http://www-dccps.ims.nci.nih.gov/ARP/breastcancer.htm. The BCSC was established to enhance our understanding of the relationship of screening practices to breast cancer mortality and currently includes data on nearly three million screening mammograms. Key activities in the expansion are to track performance of digital mammography as it enters clinical practice, obtain more detailed risk factor data and expand the diversity of the populations represented in the BCSC. Plans for establishing a Colorectal Cancer Surveillance Consortium are underway.

Tracking progress in the use of and access to recommended state-of-the science cancer treatment is central to examining progress in reducing the cancer burden. The **SEER Medicare-linked**

data (http://www-dccps.ims.nci.nih.gov/ARP/seermedicare.html), a collaborative NCI/HCFA effort initiated in 1987 to link clinical data collected by the SEER registries with claims for health services collected by Medicare, is being used for a broad array of studies including assessing patterns of care, costs of cancer treatment, and use of screening technologies in patients over 65 years of age and older. SEER-Medicare data are increasingly being recognized as a major national research resource for examining dissemination and quality of cancer care. Building on ten years of data from SEER-based studies on patterns of cancer care, NCI is now analyzing, presenting, and publishing data on trends in cancer care. Data from the first longitudinal study on quality of life among a cohort of 3,600 men living with prostate cancer are being published (http://www-dccps.ims.nci.nih.gov/ARP/PCOS/results.html). These data provide patients and their physicians a much better sense of patient centered outcomes following prostate cancer treatment, a critical element for informed clinical decision making. A major new NCI initiative, **Cancer Care Outcomes Research and Surveillance (CanCORS**), designed to support research to improve data and methods related to improving the quality of cancer care, is under development. (See Quality of Care Challenge page x.)

Improving our understanding of how physicians in the community, especially those not connected to academic medical centers, translate and apply new knowledge about cancer risk screening and treatment in the clinical setting will further enhance our understanding of where to focus efforts to improve care. Current rates of colorectal cancer screening are much too low to have a significant impact on cancer mortality in the population. **The Survey of Colorectal Cancer Screening Practices in Health Care Organizations** (http://www-dccps.ims.nci.nih.gov/ARP/ Physician/practices.html) is assessing current, nationally representative data on the physician and health system factors that may influence the use of screening and diagnostic follow-up for the early detection of colorectal cancer. In another national survey of physicians, **the Physician Survey on Cancer Susceptibility Testing** (http://www-dccps.ims.nci.nih.gov/ARP/ Physician/testing.html), data are being collected on physicians' knowledge of available genetic tests for specific cancer susceptibility genes and examining physicians' attitudes toward testing.

While the Cancer Atlas shows differences in the geographic patterns of cancer by disease site and over time, **Geographic Information Systems (GIS)** provide new tools for exploring such patterns and generating hypotheses for etiologic research. In 1999, NCI funded a prototype GIS system for breast cancer research that was piloted as part of the Long Island Breast Cancer Study. The Long Island GIS provides the opportunity to apply this powerful emerging technology to the study of possible environmental causes of breast cancer. Through a new initiative, NCI plans to support research aimed at moving the use of GIS beyond database storage and mapping to become true analytic tools for cancer research.

The development and application of modeling techniques and tools to population-based settings to answer "why" questions are essential for analyzing cancer trends. NCI has a longstanding responsibility to provide answers to critical research questions that cannot be obtained from direct observation because of expense, ethical, or other reasons. For example, a trial is only conducted in limited study populations under selected study conditions, so extrapolation to other settings and conditions may only be feasible through modeling. NCI is supporting a program called the **Cancer Intervention and Surveillance Modeling Network (CISNET),** the goals of

which are to answer the "why" questions in the analysis of cancer incidence and mortality; determine if recommended interventions are having their expected population impact; predict the impact of new interventions on national trends; and study optimal cancer control strategies. In Fiscal Year 2000 nine projects were funded, seven in breast cancer and one each in colorectal and prostate cancer. Reissuance of the announcement in Fiscal Year 2002 will target prostate, colorectal, and possible lung cancer.

A number of national efforts are ongoing in cancer and cancer control surveillance. NCI has worked for many years with its partners at other Federal agencies, such as NCHS, CDC, the Food and Drug Administration (FDA), and the Health Care Financing Administration (HCFA), to expand capacity in this critical area of health surveillance as a means of tracking progress in cancer control and providing data resources for exploring new leads in cancer etiology. One longstanding goal of NCI and the CDC has been to develop a national cancer surveillance program. In February 2000, NCI and the CDC, through a Memorandum of Understanding, formalized this long collaborative effort to **form a comprehensive, Federally integrated cancer surveillance and cancer control research system**.

The Plan

Objectives and Milestones for Fiscal Year 2002

1. **Improve cancer registry data by expanding SEER coverage, improving the quality of all population-based cancer registries, and enhancing SEER as a research resource.**

   - Support 2 to 5 newly added SEER registries to improve coverage of 5 key populations: non-Mexican Hispanics, residents of Appalachia and other rural areas, (especially those of lower socioeconomic classes), rural African Americans, American Indians, and populations with high cancer mortality rates.

   - Provide funding for technical assistance, quality control, and special studies designed to improve operational efficiency and data comparability among population-based cancer registries. This will include support for field and analytic audits; training and fellowship programs; methodology development; linkage with other health-related information sources; and development of more efficient technology-based information systems.

   - Expand support for applied innovations in SEER population-based cancer registry data systems, particularly development of portable modules that facilitate cost-effective operations, improve methodology, and advance research in newly diagnosed patients, including techniques such as rapid case ascertainment.

   - Develop a biospecimen resource for archived tissue for population-based

surveillance and epidemiologic research. Support on-staff pathologists, tissue accession managers, and administrative personnel to coordinate response to approved requests for specimens.

2. **Expand systems and methods to enhance the quality of cancer control data on risk, health and behaviors, and screening practices linked to high quality data on cancer outcomes.**

   - Build a comprehensive, integrated surveillance system with public and private partners to monitor progress in tobacco control at local, regional, and national levels. (Two initiatives budgeted in the Tobacco Extraordinary Opportunity, see page x)

   - Develop capacity for regional cancer control surveillance and area specific cancer profiles to investigate the utility of enriching data on cancer related risk and prognostic factors in areas covered by high quality cancer registration. This will be done through SEER special studies, interagency agreements with national and regional health surveillance organizations, and interagency contracts.

   - Fund surveillance screening consortia to examine the quality of cancer screening performance at the community level. Continue efforts to examine quality of mammography screening through the Breast Cancer Surveillance Consortium, begin a comparable research consortium in colorectal cancer screening, and examine need to establish comparable consortia to evaluate screening quality for cervical and prostate cancers.

   - Supplement existing population research networks, such as the Cancer Research Network, and surveillance screening consortia, to examine emerging issues in cancer control, including obtaining data on barriers to entry into cancer clinical trials, expanding surveillance of cancer screening in specific ethnic or at risk populations, and examining the effect of tobacco and food related policy and legislation.

   - Fund data collection and research on prognostic risk, health behaviors, quality of life, and the processes of cancer care, and examine how these factors relate to cancer outcomes within cohorts of cancer patients. Strengthen the methodological and empirical foundations of quality of care assessment in cancer. (See CanCORS discussion in Quality of Care, page x.)

   - Conduct SEER special studies to obtain similar cancer control and quality of care data within SEER registries; explore the feasibility of obtaining specific cancer care data currently not obtained as part of routine cancer registration.

   - Develop new data linkages and expand support for analysis of linked data sets, such as the SEER-Medicare database, managed care and other sources of

claims data, or other regional or national health surveillance data within regions with high quality cancer registration.

- Support statistical and methodological studies to improve the accuracy and reliability of data on socioeconomic determinants of cancer rates and risk, health behaviors, and screening in regional and national populations.

- Develop statistical and graphical methods, software applications, and other technologies relevant to geospatial and mapping research.

3. **Expand systems and methods to enhance capacity for exploring causes of cancer, generating new hypotheses on risk, and identifying new opportunities for cancer control interventions.**

   - Fund research studies utilizing the NCI Atlas of Cancer Mortality in the United States 1950-1994 and other population based data systems on cancer incidence, vital statistics, and vital records to identify potential new leads in cancer causation.

   - Support research initiatives using geospatial, mapping, and other analytic methods applied to existing population-based systems of environmental, sociocultural, and other relevant risk factors to develop hypotheses for more in-depth studies of cancer causation.

   - Support studies that use emerging biospecimen resources from population based cancer registries to facilitate research in cancer causes. (See Genes and the Environment Extraordinary Opportunity.)

4. **Improve and expand training in surveillance research and dissemination of information to researchers, public health professionals, the public, policy makers, advocates, and legislators.**

   - Continue to produce the annual NCI National Cancer Progress Report to improve dissemination of data on the cancer burden and progress in cancer control.

   - Improve surveillance data dissemination utilizing emerging information technologies and the Internet for information exchange. NCI will expand innovative dissemination, particularly visual representation of data to improve its comprehension by a non-technical audience.

   - Fund existing surveillance and applied research networks and consortia to conduct intensive training programs, provide sabbatical opportunities for research professionals, and initiate and develop academic curricula with a focus on surveillance research in Schools of Public Health.

TRAINING, EDUCATION, AND CAREER DEVELOPMENT

The Challenge

Training, education, and career development for the next generation of scientists remains one of our most important challenges. The scientists of the future will need to be more versatile in their use of new technologies; able to work in teams to understand the complicated environmental, genetic, and molecular variables contributing to human cancers; and better prepared to translate discoveries into public benefit. We need to implement and sustain multiple long-term strategies to attract the most talented individuals to cancer research. We need to create a stable cadre of well-trained technical, biological, behavioral, medical, and public health scientists dedicated to the cancer research enterprise. And we need to ensure that newly trained scientists can and will work together effectively to solve problems. Scientists in various disciplines can no longer operate in isolation. The interdisciplinary environment is becoming a way of life for research. Our success will depend upon our ability to move beyond traditional educational and research cultures, overcome health financing constraints, and address socioeconomic inequities that have proven to be barriers to progress in the past.

To meet this challenge, we must continue to implement training, education, and career development strategies to address five crucial issues. We must:

- **More adequately prepare basic scientists** by encouraging them to conduct research directly related to human cancer and preparing them to collaborate with clinical and population scientists and function in team research settings. Ultimately, all of our discoveries in model systems must be confirmed in human systems, and basic scientists must be prepared to make these critical contributions to cancer research.
- **Reverse the migration of medical doctors from research to practice.** This is the single most threatening consequence to cancer research of the shifting economics of the health care system. We must use more effective ways to train clinical investigators and ensure they have protected time to conduct the patient oriented research that ultimately will translate basic discoveries into better methods for cancer prevention, diagnosis, and treatment.
- **Increase the numbers and stabilize the careers of population, behavioral, and public health scientists.** The discoveries of scientists dedicated to prevention, early detection, behavior modification, and risk factor analysis will have a significant impact on reducing future cancer incidence and mortality. We must develop better ways to train these scientists to function in interdisciplinary research settings and work effectively with patient oriented and basic scientists. We also must provide them with protected time to do research.
- **Create a research establishment that is ethnically and racially diverse**. We need scientists who are sensitive to the factors that lead to disproportionate cancer incidence and mortality in underserved populations. All scientists must be better trained and prepared to conduct research that will help overcome the cultural and socioeconomic barriers responsible for the unequal burden of cancer. Demographic predictions dictate an intensified and expanded effort in this area.

- **Attract and integrate a wide array of technical and informatics disciplines into cancer research.** These disciplines are likely to be critical driving forces for future progress.

The theme for the future is to train scientists to work on problems as integrated, multidisciplinary teams. This team concept also is the foundation for NCI's creation of new centers, networks, and consortia. (See discussion of these on pages x-x of this document.)

Goal

Build a stable, racially and ethnically diverse cadre of basic, clinical, behavioral, and population scientists trained to work together effectively and use the most advanced technologies in building our knowledge base and in translating discoveries into more effective cancer prevention, detection, diagnosis, and treatment strategies.

Progress Toward Meeting the Challenge

With full implementation of NCI's Strategic Plan for Research Training and Career Development over the next few years, we expect to address the full range of training and career development needs in basic, clinical, population, and behavioral sciences in cancer research. A series of awards are being implemented to meet the career needs of new and established investigators and NCI's anticipated research priorities. Minority recruitment and engagement of Minority-Serving Institutions (MSIs) in the cancer research enterprise will be supported by new award mechanisms.

A series of career tracks follow the progress of participants through the predoctoral, postdoctoral, and initial independent junior faculty stages of their research careers. These tracks culminate when participants become established scientists with stable research funding. Special programs have focused increased resources on career tracks for M.D.s in cancer research, behavioral and population scientists, minority scientists, and scientists in highly technical fields important to the future of cancer research. NCI funds both individual and institutional awards for training and career development opportunities.

Individual Awards

- **Individual mentored five-year awards** provide opportunities for M.D.s pursuing basic or clinical research career tracks and for individuals pursuing population science career tracks.

- **Bridging awards** encourage basic scientists to engage in research directly related to human cancer and minority scientists to pursue successful careers in cancer research. These awards provide a mentored period of support and protected time for individuals to develop research programs.

- **Transition awards** provide protected time for a three-year period to new investigators to

initiate successful research programs. These awards are now in place for NCI's two most critical areas of need, medically trained doctors in basic and clinical research and population scientists. A transition award for minority scientists is scheduled to be established in 2000.

- **Established investigator awards** provide seasoned investigators in the clinical and population sciences protected time to conduct research and mentor new scientists. NCI believes that this popular award for clinical scientists will successfully curtail their migration from research to patient care in the current health care delivery system. The award for population scientists is new in 2000.

- New **diversified sciences career development awards** are designed to attract technology developers and scientists in disciplines that have not been traditionally associated with cancer research but are clearly needed for the future.

Institutional Awards

Institutional awards are five-year awards to institutions for developing and conducting training and career development programs for researchers. These awards can be designed to achieve special goals by employing specific requirements and assembling mentors who can uniquely support program objectives.

- **National Research Service Awards**, NCI's mainstay method of training basic scientists now includes special provisions for curriculum and research environments that orient all trainees to cancer related research opportunities and approaches of the future.

- **Institutional Clinical Oncology Career Development Programs** prepare the next generation of clinical scientists to design trials based on their collaborations with basic scientists.

- **Institutional Education and Career Development Programs** initiated in 2000 prepare the next generation of individuals to participate in highly collaborative, multidisciplinary team research settings. These programs are particularly suitable for the population sciences but also are already proving valuable in training molecular pathologists and imaging scientists.

- The **Continuing Umbrella of Research Experiences (Cure) Program** is designed to capture minority students at the high school and undergraduate level and proactively encourage and assist them to become independent investigators. This program relies on a spectrum of supplemental funding to institutions and career development awards.

- **Minority Institution/Cancer Center Partnerships** are designed to link over 300 Minority-Serving Institutions (MSIs) with the 60 research intensive NCI Cancer Centers to increase the number of minorities engaged in cancer research, strengthen the research capabilities of minority institutions, and increase the training, research, education, and community outreach activities of NCI Cancer Centers focused on reducing disproportionate cancer incidence and mortality in minority populations. (See page x for more information.)

By 2002, all of the above programs should be fully deployed and ready to begin fulfilling our training and career development objectives and milestones.

The Plan

Objectives and Milestones for Fiscal Year 2002

1. **Continue to provide training, career development opportunities, and protected research time to developing and established cancer scientists.**

   - Maintain a stable National Research Service Awards (NRSA) Program to train predoctoral and postdoctoral basic scientists through traditional institutional and individual awards.

   - Continue to increase the participation of clinically trained individuals in basic research and in patient oriented research by funding 20 new individual mentored awards, 30 new transition awards, and 15 new special awards that provide established scientists protected time for research and for mentoring the next generation of scientists.

   - Continue to expand the number of well-trained population, behavioral, and public health scientists in cancer research through the NRSA Program. Fund 20 new mentored awards, 20 transition awards for junior independent scientists, 10 special awards to senior scientists for protected research time and mentoring, and 10 unique institutional awards that will attract and train a new generation of team scientists.

   - Expand the existing NCI Scholars Program by funding 10 additional scholars who will develop their research on the campus and transition to an extramural institution and by initiating two new experimental training and career development programs to link the resources of the NCI Intramural Program with extramural institutions. The latter will be used to develop a critical mass of mentors and combined facilities where few institutions have the full range of required capabilities (e.g., prevention, radiation oncology).

   - Maintain Internet information services that provide full access, description, and instruction for all training and career development opportunities offered by NCI.

2. **Continue to provide and refine special training and career development opportunities that prepare new and established scientists to function in collaborative, team research settings.**

   - Increase the number of basic scientists conducting human cancer research by

funding 30 new special bridging awards that provide both a mentored training experience and transition funding for establishing a research program that interacts with clinical and/or population scientists.

- Fund 5 new Institutional Clinical Oncology Career Development Programs designed to prepare clinically trained individuals to become expert in clinical trials design and implementation dependent upon collaboration with basic scientists.

- Implement 10 new Education and Career Development Programs for population and behavioral scientists that will prepare them to work in collaborative team research settings with basic scientists and clinicians.

- Expand and initiate career development opportunities in highly specialized interactive, translational, and research consortia and networks (e.g., Specialized Programs of Research Excellence, Imaging Centers, Tobacco and Tobacco-Related Centers) that are accessible to new and established investigators.

3. Continue to integrate new technical and research disciplines into the cancer research enterprise.

- Support new specialized institutional education and career development programs that integrate traditional biomedical researchers with other non-traditional sciences (e.g., physics, engineering, informatics) and technology developers.

- Support 5 new individual Diversified Sciences Career Development Awards to attract other disciplines into cancer research for the purpose of working in multidisciplinary research settings.

4. Expand programs designed to recruit, train, and sustain underserved racial and ethnic minority individuals in cancer research and provide partnership opportunities for Minority-Serving Institutions (MSIs) with research intensive NCI Cancer Centers.

- Expand the CURE Program by increasing the number of trainee positions on institutional National Research Service Awards by 50; providing new supplemental funding to 10 Cancer Centers for high school and undergraduate student research experience; funding 10 new minority training positions in Clinical Oncology Career Development Programs; funding 10 new positions for Cancer Education and Career Development Programs in the population sciences; funding 50 new Minority Investigator Supplements to NCI research project grants; and funding 20 new mentored career development awards for basic scientists and clinically trained scientists.

- Develop and add new features to the CURE Program by funding 10 new Career

Transition Awards for basic, clinical, and population minority scientists in their first junior faculty positions and 20 NCI Cancer Centers to "broker" connections between individual minorities seeking research experiences and the scientists of the Cancer Center.

- Expand the number of planning grants and partnership grants to MSIs and NCI Cancer Centers by funding 10 collaborative planning grants focused on training and education programs, one comprehensive partnership planning grant, and two comprehensive partnerships. (The research aspect of these partnerships is budgeted under the Centers, Networks, and Consortia Challenge, Objective 1.)

- Increase access for minorities to training and career development opportunities by improving NCI Internet information services and linking to those public and private agencies that provide related services.

QUALITY OF CANCER CARE

The Challenge

More than eight million Americans will be treated for cancer in 2000, with 1.2 million having newly diagnosed cases. Direct medical care costs attributable to cancer will exceed $50 billion. The toll in human pain, suffering, and fear cannot be captured in the national cost accounts but will be keenly felt by the millions of people with cancer, their families, and community caregivers who bear the burden of cancer daily. The National Cancer Institute, which has long been at the forefront of basic and clinical research to understand the causes of cancer and translate findings into more effective interventions, now proposes an ambitious program of research to improve the quality of cancer care by strengthening the information base for cancer care decision making.

The aim is to better understand what constitutes *quality* cancer care, with an emphasis on the patient's perspective; to identify geographic, racial/ethnic, and other disparities in who receives quality care; and to strengthen the scientific basis for selecting appropriate interventions along the entire continuum of care: prevention, diagnosis, initial treatment, survivorship, and end of life. All decision makers, public and private, will benefit from this expanded information base, but special emphasis will be placed on ensuring that Federal agencies that either pay for, directly deliver, or regulate cancer care have the information they need to make quality-enhancing policy choices.

The quality of cancer care is a major national concern, as has been underscored by the National Cancer Policy Board's Institute of Medicine report, *Ensuring the Quality of Cancer Care*; the 1999 report of the President's Cancer Panel on cancer care quality; and initiatives undertaken recently by a number of organizations (e.g., the American Society of Clinical Oncology). From these disparate analyses and proposals for change, NCI sees an emerging consensus about the critical elements of a research agenda to improve the quality of cancer care.

First, we need a core set of cancer care measures that are patient-centered, acceptable to providers and payers, span the continuum of care, and meet the highest technical standards of validity, reliability, and sensitivity to change. These endpoint measures would greatly enhance our ability to compare interventions across studies and over time. Equally important, we need a comprehensive, critical evaluation of existing practice guidelines to develop a baseline understanding of what providers and payers currently considered being "quality" cancer care.

Second, we must strengthen the data and methods "infrastructure" for conducting an important range of quality of care analyses. These include studies to determine which interventions improve patient-valued outcomes (thereby enhancing the quality of care); to identify geographic or racial/ethnic variations in receipt of quality care; and to monitor quality over time, both at the individual and population level. Indeed, the National Cancer Policy Board has recommended the development of a national cancer data system to support such studies on an ongoing basis. For this to happen successfully, there must be close cooperation among a number of public and private entities, including community-based and hospital-based tumor registries and the

organizations that support their efforts. If such a national cancer data system is to reach its full potential for quality of care analysis, it must have the sustaining support of public agencies and private organizations working in concert to improve both the community representativeness of the data and the rigor and relevance of the analyses.

Third, it is critically important to determine whether therapies shown to be efficacious in clinical trials have been incorporated successfully into community practice. If so, what were the key factors that made it happen? If not, what explains the failure to turn good science into good medicine? In addition, there should be a critical examination of whether, when, and how NCI-sponsored trials, which have been the backbone of the clinical discovery process in cancer, should give greater emphasis to patient-centered outcomes in addition to the important traditional endpoints of survival and tumor progression.

Finally, the quality of cancer communications – between patient and provider, the news media and the patient, and the patient's family and the third-party payer, to note three salient cases – is a central determinant of cancer care quality. We must have a better understanding of the information needs of patients, families, and other decision makers involved in the choice of cancer interventions. Based on that understanding, we must develop practical toolkits and other innovative approaches to enhancing access to relevant information for cancer care choices.

NCI's proposed program of research responds directly to the challenges posed in this emerging consensus about how to improve the quality of cancer care. In presenting an initial design of the research program to DHHS Secretary Donna Shalala, NCI urged that cancer be made a "working model" for quality of care research *and* application. The Secretary responded by approving the creation of the Quality of Cancer Care Committee (QCCC), a trans-agency task force with representatives from Federal agencies involved in cancer care delivery (e.g., the Department of Veterans Affairs), coverage (e.g., the Health Care Financing Administration), and regulation (the Food and Drug Administration). In addition, the NCI quality of care initiative now operates organizationally within the Secretary's larger Quality Improvement Initiative, in close coordination with the Agency for Healthcare Research and Quality. In all of these efforts, NCI expects to benefit significantly from the experience acquired in supporting, and participating directly in, a number of quality-related projects over the past decade (see *Progress Toward Meeting the Challenge* below to learn about some of these efforts).

The National Cancer Institute understands the importance of ensuring that the tremendous scientific advances in preventing, detecting, treating, and curing cancer are translated into interventions that are shown to extend and improve quality of life for the millions of individuals and families who not only bear the burden but carry the hope. For this to occur, sustained collaboration will be essential not only among Federal researchers and policy makers, but among public agencies and the full spectrum of private entities involved in cancer care -- providers and third-party payers, professional associations, patient advocacy groups, and organizations that measure and monitor quality of care at the behest of private and public decision makers.

NCI's quality initiative will be an important early step in support of such sustained collaboration. Moreover, while this research program is clearly cancer-focused, it should deepen our understanding of how to define, monitor, and improve the quality of health care overall.

Goal

Enhance the state of the science for defining, monitoring, and improving the quality of cancer care *and* inform Federal-level decision making on cancer care delivery, coverage, and regulation.

Progress Toward Meeting the Challenge

We believe that establishing NCI's quality of cancer care research initiative and the QCCC, consistent with the Secretary's Quality Improvement Initiative, will prove to be landmark events in the growth of knowledge about quality in cancer care and in our ability to provide quality care to people with cancer and those at risk. The newly launched **Cancer Care Outcomes Research and Surveillance Consortium (CanCORS)** is the central vehicle in NCI's quality initiative for studying the impact of targeted interventions on patient-centered outcomes, investigating the dissemination of state-of-the-science therapies into community practice, examining the influence of modifiable risk factors, and analyzing disparities in the delivery of quality cancer care. Focusing on the four most prevalent disease sites (breast, prostate, lung, and colorectal), CanCORS multi-center teams will work collaboratively to conduct large (N=6,000-8,000) observational cohort studies of newly diagnosed cancer patients. These analyses will support recommendations for an expanded core set of data elements that should be collected routinely by tumor registries, in support of a national data system to monitor the quality of cancer care. CanCORs teams may also examine major methodological issues in outcomes research conducted in community settings.

However, the issues of quality are not new to NCI; the Institute has long had in place both programmatic and organizational mechanisms essential to pursuing important research questions related to quality of care. Since 1973, the **Surveillance, Epidemiology, and End Results (SEER) program** (http://www-seer.ims.nci.gov/) has provided an essential foundation for studying quality issues by monitoring the national cancer burden and providing an indispensable data resource for assessing the impact of research advances on cancer outcomes. For example, **SEER patterns-of-care studies** have shown that breast conserving surgery for early stage breast cancer increased between 1987 and 1995 for women of all ages, but that older women were less likely to receive post-surgical radiation therapy. **Studies linking SEER and Medicare data** have shown that rates of surgical treatment for early stage lung cancer, and survival, were lower for black patients compared with white patients. The **Prostate Cancer Outcomes Study**, initiated in 1994, is using data from six SEER registries to conduct the first systematic evaluation of the impact of treatments for primary prostate cancer on the quality of life of men living with this disease (http://www.dccps.ims.nci.nih.gov/ARP/PCOS/index.html).

NCI's **Applied Research Program (ARP)** (http://www.dccps.ims.nci.nih.gov/ARP/index.html) is an established locus of key NCI research on quality issues. In addition to its involvement in the SEER-related efforts described above, the ARP has recently launched the **HMO Cancer Research Network** (http://www-dccps.ims.nci.nih.gov/ARP/hmo.html), which promotes collaborative cancer research among health care provider organizations. Supported by the first award under this program, a consortium of researchers affiliated with 10 major not-for-profit

HMOs will, in addition to other activities, conduct studies of late stage breast and invasive cervical cancer cases to identify patient, provider, and system factors that contribute to preventing advanced disease, and also will study the quality and impact of smoking cessation programs delivered in HMOs. In 1999, NCI established an **Outcomes Research Branch** within the ARP to provide a focal point for this research (http://www.dccps.ims.nci.nih.gov/ARP/outcomes.html).

Other NCI initiatives to elucidate quality of care issues in cancer include the **Breast Cancer Surveillance Consortium**, which each year examines the performance of screening mammography for thousands of at-risk women and cancer patients in eight community settings across the U.S.; the newly developed **Colorectal Cancer Surveillance Consortium** (see Trends Challenge for additional detail); and the **Black-White Cancer Survival Study** (see Health Disparities Challenge).

The Plan

Objectives and Milestones for Fiscal Year 2002

1. **Develop core process and outcome measures for assessing the quality of cancer care.**

   - Establish a national panel of experts in cancer outcomes measurement theory and practice to evaluate existing endpoint measures and instrumentation and recommend a core set of valid, reliable, sensitive, and feasible clinical and patient-centered endpoint measures for use in studies assessing the quality of cancer care.

   - Evaluate published practice guidelines and care maps produced by major professional organizations, medical care providers, third-party payers, and researchers that describe "quality" cancer care for each of the most prevalent disease sites (breast, prostate, lung, and colorectal) and across the full continuum of care.

2. **Strengthen the methodological and empirical foundations of quality of care assessment in cancer.**

   - Sustain support for CanCORS studies of the impact of targeted interventions on patient-centered outcomes, dissemination of state-of-the-science therapies into community practice, the influence of modifiable risk factors, and disparities in the delivery of quality cancer care.

- Increase support for analyses of the linked SEER-Medicare database to investigate the diffusion and outcomes impact of selected cancer interventions among individuals aged 65 and older, with special emphasis on interventions whose differential application may contribute to cancer outcome disparities.

- Support the creation of databases that link tumor registry information with private payer administrative data for individuals under age 65 to expand capacity to investigate the diffusion and health outcomes impact of selected cancer interventions among the non-elderly.

- Sponsor innovative economic and health services research studies on the impact on patient-valued outcomes and economic costs of cancer prevention, control, and screening interventions to improve the application of cost-effectiveness and outcomes analysis in cancer prevention and screening trials and community cancer prevention and control interventions.

- Sponsor new investigator-initiated studies to strengthen the methodological foundations of outcomes research and quality of care assessment.

3. **Enhance quality of care research within the restructured NCI clinical trials program.**

   - Sponsor a symposium and follow-on workshops to bring together leading researchers, patient advocates, and the relevant Federal agencies to assess the current state of the art, identify key research questions, and develop a decision strategy for encouraging comprehensive assessments of patient outcomes in clinical trials.

   - Expand support for studies of diffusion patterns, and the overall diffusion rates of important clinical trial findings into community practice. Focus on factors that accelerate or impede the use of new therapies and geographic or population group differences in the their availability or adoption. Building on study findings, develop a process for incorporating successful diffusion techniques into clinical trials design and communicating trial results to the public and medical community.

4. **Improve the quality of cancer care by strengthening the quality of cancer communications.**

- Gather nationally representative data to assess the current status of cancer communications and better understand the amount and quality of information now available and being used in cancer care decision making. (See Cancer Communications Extraordinary Opportunity.)

- Within the Centers for Excellence in Cancer Communications Research, support projects to evaluate and enhance cancer communications' effectiveness in helping patients understand the risks and benefits of interventions and in improving overall quality of care. (See Cancer Communications Extraordinary Opportunity.)

- Provide supplemental funding to Community Clinical Oncology Programs (CCOPs) for pilot projects to identify information needs of cancer patients, survivors, and their families and develop new communications strategies to improve cancer care decision making, particularly in vulnerable populations.

- Create new communications products and tools for cancer patients and their caregivers, individuals at elevated risk, advocacy groups, health care professionals, third-party payers, and public agencies that improve the accuracy, clarity, and timeliness of cancer care decision making. (See Cancer Communications Extraordinary Opportunity.)

5. Ensure that Federal decision making on cancer care is informed by the best available scientific evidence about quality.

- To identify and meet Federal agency needs for cancer care information, continue to convene the QCCC; support and participate in inter-agency collaborative demonstration projects on quality measures and assessment.

REDUCING CANCER-RELATED HEALTH DISPARITIES

The Challenge

Profound advances in biomedical science have occurred over the past several decades, which for many Americans have contributed to increased longevity and improved quality of life. Despite this progress, however, the burden of disease is not borne equally by all population groups in the United States. For example, the death rate from prostate cancer among African American men is almost twice that of white men, whereas stomach cancer mortality is substantially higher among Asian-Pacific Islanders, including Native Hawaiians, than other populations. Cervical cancer incidence in Hispanic women has been consistently higher at all ages than for other women, although African American women have the highest death rate from cervical cancer. Persons of low socioeconomic status have higher death rates for most cancers than persons of higher socioeconomic status. Overall, men are about 50 percent more likely than women to die from cancer.

Disease always occurs within a context of human life circumstances. These circumstances, which include social position, economic status, culture, and environment, are critical determinants of who is born healthy, who grows up healthy, who sustains health throughout their life span, who survives disease, and who maintains a good quality of life after diagnosis and treatment. In particular, social injustice, through its impact on absolute and relative poverty, racial/ethnic discrimination, risk-promoting lifestyles, and environmental exposures, has to a large extent created the health disparities that currently exist in the United States. **The unequal burden of disease in our society is a challenge to science and a moral and ethical dilemma for our Nation.**

The relative importance of these social causes to the development of cancer-related health disparities, and their relation to factors that lead to unequal access to high quality cancer diagnosis and treatment, must be explained if we are to reduce these health disparities. To do this, we must increase fundamental research into the social causes of health disparities, the psychosocial factors that mediate them, and the biologic pathways that can explain their impact.

As we study the complex determinants of cancer-related health disparities through fundamental cancer control research, the relative importance of different determinants will vary depending upon where in the disease process disparity appears. A key question is: How can we best measure and monitor cancer-related health disparities across the spectrum of cancer incidence, stage of disease at diagnosis, disease recurrence, quality of life, and cancer mortality? Research to address this question will build on the expansion of the Surveillance, Epidemiology, and End Results (SEER) program to include more diverse U.S. populations and better measures of socioeconomic status, environmental exposures, and other critical factors.

While fundamental and surveillance research will shed light on the complex determinants of cancer-related health disparities and how best to monitor them, another key question is the extent to which prevention, early detection, treatment, and communication interventions can effectively

reduce, if not eliminate, cancer-related health disparities. Consistent with the recommendations of the Institute of Medicine's report, *The Unequal Burden of Cancer,* and the Healthy People 2010 goal to eliminate racial and ethnic health disparities, the National Cancer Institute is strongly committed to an intervention research program that will address cancer health disparities across the cancer control continuum from prevention to end of life care.

NCI has developed an initial research framework (Figure 1) that reflects the growing evidence that socioeconomic, cultural, health care provider, institutional, and environmental factors contribute substantially to cancer-related health disparities.

Figure 1

The elements that influence health disparities are complex, and their interactions are largely unknown. While health disparities have been framed historically in the context of racial and ethnic disease differences, racial and ethnic classifications have always been socially and politically determined and have no basis in biological science. Moreover, social injustice, disproportionately experienced by specific racial and ethnic groups, is profoundly linked to the social determinants of the unequal burden of disease. The power of scientific discovery must be used to elucidate the meaning and effect of the human circumstances in which differential disease burdens occur.

Finally, in our national effort against cancer, there is a critical disconnect between scientific discovery and cancer care delivery; this disconnect is itself a key determinant of the unequal burden of cancer in our society. **Barriers that prevent the benefits of research from reaching all populations, particularly those who bear the greatest disease burden, must be identified and removed.** Thus, scientific discovery, while absolutely necessary, is not sufficient. The NCI currently devotes resources toward the application of research discoveries through education and training programs. In response to this challenge, we will develop new intergovernmental and public/private partnerships to expand the dissemination and diffusion of evidence-based interventions and encourage the development of health care policies that will improve health and well being in underserved communities.

Goal

Understand the causes of health disparities in cancer and develop effective interventions aimed at reducing or eliminating these disparities.

Progress Toward Meeting the Challenge

NCI has long been aware of, and concerned about, disparities in cancer incidence, morbidity, and outcome among various population groups in our country. Even prior to designating Cancer-

Related Health Disparities as a key challenge for the Institute, NCI established a variety of infrastructures and initiatives to improve our understanding of these disparities and to develop strategies and interventions to address them. These activities have provided a firm foundation from which to launch our new and intensified efforts, described in detail in **NCI's Strategic Plan to Reduce Health Disparities** (add link).

For example, NCI's **SEER cancer registry program** (http://www-seer.ims.nci.gov) has been expanded to cover more of the racial, ethnic, and socioeconomic diversity of the United States, allowing for better description and tracking of cancer-related health disparities. Methodologic studies are seeking better ways to measure socioeconomic factors and determine their relationship to cancer incidence, survival, and mortality. NCI supports a growing body of research on health disparities across the cancer continuum; coordination of this research has been enhanced by establishment of the **Applied Sociocultural Research Branch** (http://dccps.nci.nih.gov/ASRB/Asrb2/default.html) within the Division of Cancer Control and Population Sciences. Recognizing the broad relevance of this research to other disease outcomes, NCI collaborates with other Federal agencies in supporting important research initiatives, including co-funded research with the Agency for Healthcare Research and Quality (AHRQ) under their initiative, "Understanding and Eliminating Minority Health Disparities."

NCI's **Office of Special Populations Research (OSPR)** (http://ospr.nci.nih.gov) has been a focal point for leadership and coordination on research addressing the cancer-related concerns of underserved and other vulnerable populations. OSPR administers a variety of outreach and other programs targeting specific special populations. Its newest initiative is the **Special Population Networks for Cancer Awareness, Research and Training (SPN)**, a network of 17 institutions that will create and implement cancer control, prevention, research, and training programs in minority and underserved communities. In the Network's initial phase, a variety of cancer awareness activities are being implemented in targeted communities, and community groups are working with private and public sector organizations to develop project plans. (http://ospr.nci.nih.gov/networks.html)

The **Comprehensive Minority Biomedical Program (CMBP)** aims to increase the number of minority scientists in biomedical research and to enhance the careers of those already in the field. CMBP programs include NCI's newest training initiative for underserved minorities, the **CURE Program (Continuing Umbrella of Research Experiences)**, and a host of other training opportunities targeting high school students through established researchers. NCI believes that improving the representation of ethnic and minority individuals in research and clinical care is crucial to ensuring that important research questions concerning disparities are investigated and that discoveries are translated into community practice. (See Training Challenge for a more detailed description of NCI training initiatives targeting special populations.)

NCI also believes that greater participation of minority health professionals in clinical trials is essential to our efforts to explore research questions about cancer-related health disparities. The **Minority-based Community Clinical Oncology Programs** have for many years sought to address clinical research questions relevant to the disproportionate cancer burden experienced by specific populations. NCI also has established **collaborations with key minority professional**

organizations to increase participation of physicians from underserved populations in cancer treatment and prevention trials.

NCI's **Office of Liaison Activities** was established to provide a consistent point of contact with diverse consumer constituencies, to ensure that we are cognizant of cancer-related issues affecting specific population groups. In addition, NCI has convened a **Special Populations Working Group** to bring the expertise of individuals in the community to bear in assessing the research questions that should be addressed.

All of NCI's efforts to elucidate cancer-related health disparities are closely related to our initiatives to improve the quality of care for people with cancer and those at risk for the disease. See the Quality of Cancer Care Challenge for discussion of our progress in quality of care research and interventions.

The Plan

Objectives and Milestones for Fiscal Year 2002

1. **Create a new and comprehensive plan to organize, coordinate, and monitor NCI activities in health disparities research, education and health services support.**

    - Create a Center for Cancer Health Disparities (CCHD) headed by the Associate Director for Health Disparities reporting directly to the Director, NCI. The Center will direct implementation of NCI's strategic plan to reduce cancer-related health disparities and focus on the critical task of translating discovery into delivery to reduce these disparities

    - Develop a series of meetings, workshops, and working groups to assist in refining and implementing an agenda for reducing cancer health disparities. Also use these mechanisms to identify and support successful research activities, facilitate dissemination of new discoveries, and monitor their success in reaching agreed-upon goals.

2. **Improve capacity and accelerate knowledge through fundamental cancer control and population research.**

    - Create 4 Centers for Population Health to: (1) expand understanding of social environmental causes of cancer health disparities and psychosocial, behavioral, and biological factors that mediate them, (2) develop hypotheses for cancer control research at individual, social, institutional, and policy levels, and (3) develop, apply, evaluate, and disseminate interventions to improve cancer outcomes and reduce outcome disparities.

    - Expand ongoing epidemiologic investigations to explore racial/ethnic

cancer disparities in the United States, including studies of cancers in which these disparities are greatest (e.g., breast, cervix, kidney, prostate). Also conduct new methodologic studies to evaluate factors influencing recruitment and participation of underserved populations in cancer epidemiology studies.

3. Expand our ability to define and monitor cancer-related health disparities.

- Support 2 to 5 new SEER registries to improve coverage of 5 key populations: non-Mexican Hispanics, residents of Appalachia and other rural areas (especially those of lower socioeconomic classes), rural African Americans, American Indians, and populations with high cancer mortality rates. (See Studying Emerging Trends in Cancer Challenge.)

- Enhance national and regional data systems to measure health disparities in cancer-related health behaviors and screening practices. Expand support for cancer control supplements to the National Health Interview Survey, the California Health Interview Survey, and other regional surveys expand information on socioeconomic and other demographic factors associated with disparate cancer outcomes. (See Studying Emerging Trends in Cancer Challenge.)

- Expand methodologic research, geographic analyses, and modeling of the unequal burden of cancer.

- Enhance national and regional tobacco surveillance to improve capacity to identify and understand emerging disparities in tobacco use, particularly among high risk youth. Collaborate with Federal and non-Federal partners to explore how individual consumption patterns, health policies, legislative, taxation, and farm policies may affect tobacco use disparities. (See Tobacco Extraordinary Opportunity.)

4. Expand cancer control intervention research in prevention, early detection, treatment, and communications.

- Expand Special Population Networks for Cancer Awareness, Research and Training (SPN). Fund an additional 4-6 SPN sites to enhance research infrastructure and training in underserved communities. Partner with academic Cancer Centers to continue developing and testing community-based, participatory cancer control interventions addressing disparities. Provide additional funds for pilot developmental cancer control research projects within SPN.

- Supplement funding to existing Transdisciplinary Tobacco Research Centers (TTURCs) to study differential tobacco use patterns and quitting

among underserved populations and support development of more effective interventions to reduce the burdens associated with tobacco use.

- Expand colorectal cancer screening use and follow-up research. Conduct new intervention research to identify and overcome sociocultural and health care system barriers to the continuing under-use of fecal occult blood testing (FOBT) and flexible sigmoidoscopy, and to address comorbid illness and other barriers to appropriate clinical follow-up of abnormal FOBT findings.

- Expand research on breast and cervical cancer screening for women who have never been screened and those who are not screened regularly. Support new intervention research to identify barriers to screening for women who under-use or never-use breast and cervical screening and address sociocultural determinants in planning, implementing, and evaluating these interventions.

- Strengthen the methodologic and empirical foundation of quality of care assessment in cancer, including analysis of disparities in who receives quality cancer care, to improve understanding of the relative importance of unequal access and treatment differences as determinants of disparate cancer outcomes compared to other broader social determinants of these disparities. (See Quality of Cancer Care Challenge.)

- Provide supplements to Cancer Centers and other research awardees to expand research on health disparities in survivorship, including ethnic, cultural, socioeconomic, and institutional factors affecting the context, quality, and length of cancer survivorship in underserved communities and strategies to help cancer patients and their families make the transition to extended and long-term survivorship.

- Establish formal affiliations between NCI Cancer Centers and Minority-Serving institutions. (See Centers, Networks, and Consortia Challenge)

- Provide up to 3 years of supplemental funding to P30 Cancer Center Support Grant holders to stimulate cancer-related health disparity research, particularly in NCI-funded Cancer Centers located in or near underserved communities that experience the heaviest burden of cancer.

5. Expand the channels for research dissemination and diffusion (RDD).

- Work with the Centers for Disease Control and Prevention (CDC) and the American Cancer Society (ACS) to model and monitor the impact of research dissemination and diffusion on DHHS Year 2010 health promotion objectives generally and on cancer-related health disparities in particular.

- Facilitate adoption of evidence-based cancer control interventions through: collaborative (NCI, CDC, ACS) review of cancer health disparities objectives; consensus on indices of dissemination and diffusion program impact; identification of the most useful formats for presenting intervention research evidence; annual reviews of published evidence on best practices to reduce disparities; and publishing/posting intervention evidence reviews and best practices on NCI's Dynamic Evidence in Cancer Control Web site.

- Conduct Pilot Research to Overcome the Digital Divide (PRODD). (See Cancer Communications Extraordinary Opportunity)

- Build special dissemination and diffusion partnership programs to reach underserved communities, test these programs' value in reducing health disparities in underserved communities, and make successful pilot programs available for use by regional and local public health and cancer organizations nationwide.

- Provide one-year competitive supplements to investigator-initiated intervention research grants. Create a supplemental funding mechanism to develop and implement a dissemination and diffusion plan for interventions proven by the original intervention research to be effective in reducing health disparities.

6. Strengthen training and education in health disparities research.

- Develop a new track in the Cancer Prevention Fellowship Program to increase the number of scientists studying health disparities. Recruit 2 fellows per year to focus on health disparities research within OSPR and the DCCPS.

- Expand community-based, cancer control research training with underserved communities. Encourage Cancer Centers to partner with community organizations and health care institutions in underserved communities in order to apply for R25 training grant support for community-based clinical and cancer control research training opportunities in health disparities research.

- Expand programs to recruit, train, and sustain underserved racial and ethnic minority individuals into cancer research and provide partnership opportunities for minority-serving institutions with NCI-supported Cancer Centers. (See Training, Education, and Career Development Challenge.)

Spotlights on Research

Understanding the Cellular Changes That Lead to Cancer

For years, cancer researchers have used a somewhat scattershot approach to "create" cancer cells in the laboratory. By exposing normal cells to x-rays or chemicals, scientists can alter genes in normal cells and produce cancer cells that can be used to study cancer biology or to test the effectiveness of potential prevention or treatment drugs. Yet, this approach has a significant limitation: When altering these normal cells, scientists have little idea of or control over the kinds of genetic flaws being introduced. And, without knowing the steps involved in the start of human cancer – the specific changes that initially transform a normal cell to cancer – they have had little opportunity to develop drugs that target these steps and block or arrest cancer's development.

Until recently. In a landmark study – the culmination of 15 years of work– a team of cancer researchers "built" a cancer cell in the laboratory, determining that the introduction of only three genes is sufficient to generate a human cancer cell. In building the cancer cell, the researchers first artificially stimulated production of a telomerase catalyst, which allows cells to divide indefinitely. They then added an excess of the *ras* oncogene, common to many human cancers, which promotes cellular growth. Finally, they introduced a gene to disable two tumor-suppressing proteins. With this information, cancer researchers now have the critical opportunity to pursue a new approach to drug development, looking for agents that target these pathways and thwart cancer's growth. And, although this approach was developed using skin and kidney cells, it can now be attempted with other cell types, allowing researchers to identify the specific genetic flaws associated with cancer in a variety of cells – such as those from the breast or colon – and to develop treatments based on this information.

Identifying the specific cellular pathways that define human cancers also is enabling scientists to replicate these changes in the genes of mice. In doing so, scientists have been to induce tumors in mice that accurately mimic human cancer. And, they are finally able to test whether molecular changes associated with human cancer actually cause cancer's progression and behavior. To accelerate the output of these breakthroughs, and to use them to discover and test ways of preventing and curing cancer, NCI has established the Mouse Models of Human Cancers Consortium, an international collaboration of over 70 institutions. This consortium will support the development and validation of mouse models for human cancers.

Harnessing the Immune System to Prevent and Treat Cancer

Over the past century we have gained considerable knowledge about how the immune system fights off foreign invaders and how cancer eludes this defense system. The application of this knowledge to creating immunotherapies, such as immunotoxins and vaccines, that harness the power of the immune system to treat or prevent cancers is yielding promising results.

Recent research shows that an immunotoxin (LMB-2), a type of treatment created by linking a monoclonal antibody to a deadly toxin, may be effective against hairy cell leukemia a rare cancer of immune system B cells. When given to a patient, the antibody portion of the immunotoxin homes in on a cancer cell, attaches to it, and then delivers its poison directly to the cell, thus killing it. In a phase I clinical trial* of LMB-2 NCI researchers saw anti-tumor activity against a variety of malignancies including chronic lymphocytic leukemia, Hodgkin's Disease, cutaneous T-cell lymphoma, and most strikingly hairy cell leukemia (HCL). Four out of four HCL patients who received the LMB-2 responded to the treatment. One patient had a complete remission that has lasted almost two years and the other three patients had 98 to greater than 99 percent reduction in malignant cells circulating in the blood. Phase II trials of LMB-2 will begin soon.

Vaccines are another type of immunotherapy. Prevention vaccines, like the polio vaccine or childhood immunizations, evoke an immune response before infection strikes creating antibodies that will later ward off a challenge. Prevention vaccines for cancer are similarly designed to target cancer-causing agents, such as the sexually transmitted human papillomavirus (HPV) which is linked to over 90 percent of cervical cancer cases worldwide. HPV is now believed to cause some types of oral cancers, too, such as tumors found in the tonsils. Researchers are hoping that inoculation with inactivated HPV particles will enable the immune system to recognize and establish a defense against the virus. Worldwide, at least six vaccines with potential to prevent HPV infection are being developed and tested. NCI has launched early clinical trials of a vaccine that creates a protective effect by employing virus-like particles from HPV-16, the form of the virus involved in over 50 percent of cervical cancer cases. Preliminary results show that a low-dose injection of the vaccine induces high levels of protective antibodies against HPV. Future clinical trials may include oral cancer patients. In addition we are working on creating a chimeric vaccine that contains virus-like particles from the four major strains of HPV that together contribute to more than 80 percent of all cervical cancers.

Unlike the HPV vaccine, most cancer vaccines are designed to treat cancers by inducing an immune response that leads to a direct attack on tumor cells. For example, researchers have developed and are testing a B-cell lymphoma vaccines that primes a patient's immune system to seek out and destroy tumor cells. To create this vaccine, scientists removed tumor cells from a patient's lymph nodes and selected a protein present only on the cancer cells. The selected protein was then joined to a carrier protein which could transport it into the body and aid in creating an immune response. Finally, an immune system boosting drug was also added to the vaccine combination for maximum effect. Of the 20 patients injected with custom-made vaccines as part of a small Phase II trial, 18 remained in complete remission an average of four years. A large-scale trial of the vaccine has now been launched involving 390 patients.

Immunotherapy research has proved that the immune system can be primed to recognize and destroy tumor cells with minimal toxicity as compared with chemotherapy and other treatments. Thus, immunotoxins and vaccines are a positive addition to our arsenal of anti-cancer therapies, but additional clinical trials are needed to help us maximize their potential.

* See page X for an explanation of clinical trials.

A New Detection Tool – Looking for DNA Mutations

When we are able to detect cancer early, we can save lives. But finding a tumor in its earliest stages of development, when it is composed of only a few cells, is like searching for a needle in a haystack. Scientists funded by NCI's Early Detection Research Network (See p. x.) have developed a novel approach to early detection based on identifying genetic mutations found in the DNA housed in a cell's mitochondria – the specialized parts of a cell responsible for generating energy.

The scientists found that mitochondrial DNA mutations observed in body fluids were identical to those found in primary tumors. The researchers first analyzed mitochondrial DNA from bladder, head and neck, and lung cancer tumors and identified specific mutations linked to these cancers. Then they studied urine, saliva, and cells washed from the lungs of twenty patients with these cancers in search of similar mutations. The researchers detected mitochondrial mutations in all of the bladder and lung cancer tumors and most of the head and neck cancer tumors. In the past, researchers had found matching mutations in primary tumors and in body fluids when looking at DNA from the nucleus. However, a cell's nucleus contains only one copy of DNA. In contrast, many mitochondria exist in all cells so there are multiple copies of mitochondrial DNA within each cell making mitochondrial mutations are much easier to find and potentially more ideal avenues for detection.

The researchers envision using their discovery mitochondrial DNA for cancer screening. For example, someone at higher risk of developing lung cancer because of a history of smoking could provide his or her doctor with a sputum sample. The initial sample would be analyzed to obtain a baseline description of the individual's mitochondrial DNA. In subsequent visits, new sputum samples would be collected and compared to the baseline for changes. If changes in the mitochondrial DNA indicating cancer were observed, doctors would be in a better position to intervene while the cancer is in an early stage. The search for mitochondrial mutations in a variety of tumors represents an opportunity for developing new, non-invasive screening approaches for cancer that rely on analysis of easily collected body fluids.

Diffuse Large B-Cell Lymphoma: A Disease Within A Disease

Each year, 25,000 people in this country are diagnosed with diffuse large B-cell lymphoma (DLCBL), the most common form of non-Hodgkin's lymphoma (NHL). DLCBL is a form of cancer in which B cells in the immune system proliferate uncontrollably. Physicians have long questioned why standard chemotherapy cures only 40 percent of their DLCBL patients while the majority relapse and die. A team of scientists recently used the powerful new DNA microarray technology to make an intriguing discovery which has provided a critical understanding for solving this puzzle.

The scientists created a novel microarray tool which they labeled the "lymphochip" by mining the Cancer Genome Anatomy Project (CGAP) database for more than 18,000 genes important to

both lymphoid malignancies and the immune system and placing them on a device similar to a computer chip. The lymphochip enabled them to compare gene activity of normal and cancerous B cells and generate gene expression profiles, or signatures, of the different cell types. After examining several different forms of non-Hodgkin's lymphoma, the scientists discovered that DLBCL showed two distinct patterns of gene expression, suggesting that this diagnosis has lumped together *two* subtypes of NHL. While unable to distinguish one from the other under a microscope, the tool conventionally used for diagnosis and cell typing, scientists now are able to use advanced technology to sort out these two biologically distinct subtypes of lymphoma and to subsequently identify two distinct clinical courses that DLBCL can take. Although more research is needed, scientists are optimistic that expression signatures will lead them to more precise diagnoses and ultimately to more effective treatments for specific subtypes of this disease.

We expect over the coming years to be able to use gene expression signatures like these to vastly improve our ability to diagnose, classify, and treat not only lymphoma but all types of cancer. By analyzing differences at the molecular level as opposed to examining cells under a microscope, we can identify the genes and cell pathways that are important to cancer development and progression. These molecular differences will provide the clues to early detection and diagnosis and are the targets of present and future cancer drugs.

People's Story:
Adult and Pediatric Brain Tumors

I was diagnosed with a brain tumor six months ago. As frightening as it can be to have a brain tumor, I know I'm lucky that my mine is one of the less aggressive types.

There are more than 100 types of central nervous system (CNS) tumors. Some are highly aggressive and rapidly fatal, while others grow slowly and may be present for years before the patient feels any effect. People with very slow-growing tumors may live with them for decades and eventually die of an unrelated cause.

CNS tumors differ from other solid tumors because those originating in the brain or spinal cord (primary tumors) rarely spread to other parts of the body. More than 35,000 of these primary tumors are diagnosed each year,[1] 16,500 of which are cancerous.[2] It has been estimated that as many as 170,000 people develop metastatic CNS tumors each year from cancer cells that have migrated from a primary tumor elsewhere in the body. CNS tumors in children often form in different areas and from different cell types than in adults, and children's tumors may have a different prognosis and treatment. CNS tumors of all types cause approximately 13,000 deaths each year.

The outlook for a person with a brain or CNS tumor can depend almost as much on the tumor's location as its type. For example, a slow-growing ("benign") tumor can become life-threatening if it begins to crowd a crucial area of the brain and cannot be removed or treated, while a more aggressive tumor that is in a less critical location or more easily treated may pose less threat to the patient.

My brain tumor was discovered after I had a seizure, but I've learned people can have a very wide variety of symptoms.

Brain and CNS tumor symptoms vary markedly depending on the tumor's type and location. Headaches (particularly morning headaches), seizures, and mental changes such as memory, speech, and communication problems are symptoms that may signal a CNS tumor, or may be related to other medical conditions. Similarly, some people with a tumor that is causing excess pressure in the skull may experience nausea or vomiting, blurred or double vision, hearing disturbances, or problems with muscle control or coordination. These symptoms, too, may be related to other medical problems, so people who experience such symptoms should not assume they have a CNS tumor.

---

1 Central Brain Tumor Registry of the U.S.

2 NCI Surveillance, Epidemiology, and End Results (SEER) cancer registry program.

The doctor was able to remove most of my tumor, and we're treating the remaining part with radiation. I'm also going to try a new type of chemotherapy, but I know it may not get rid of my tumor forever.

Continuing advances in imaging technologies are improving our ability to diagnose CNS tumors and remove them more safely. Currently, magnetic resonance imaging (MRI) is the preferred test for diagnosing certain types of CNS tumors, but computed tomography (CT) is often used because it is more widely available and less expensive. Positron emission tomography (PET) is one of several other scans now used to augment MRI or CT, but these other scans require the use of scarce equipment and are costly. Researchers are evaluating new, noninvasive modalities for tumor assessment, such as magnetic resonance spectroscopy (MRS), which is available with routine MR imaging equipment. Image-guided surgery has improved the surgeon's ability remove tumor tissue without interfering with crucial brain functions. New techniques such as functional MR imaging that shows brain areas involved in motor control, sensory function, language, and other functions, are improving surgical precision even further.

After surgery, many patients are treated with radiation. Several types of radiation therapy are available, including conventional external beam radiation, and both stereotactic radiotherapy and intensity modulated radiation therapy (IMRT), which are used to treat very small, multiple, and hard to reach tumors. The gamma knife is a radiotherapy that may be used to treat certain tumors that are inoperable using conventional surgery.

Chemotherapy for CNS tumors has been hampered by problems in getting anti-cancer drugs across the blood-brain barrier, a network of vessels and cells that filter blood going to the brain. Researchers are developing new drug delivery techniques and new agents that can cross the blood brain barrier. For example, agents have been developed that temporarily open the blood-brain barrier while chemotherapy is administered through a vein or artery, and biodegradable wafers filled with chemotherapy drugs can be placed directly into the tumor. Chemotherapy drugs now include those designed to kill tumor cells, and others that inhibit the development of blood vessels that feed the tumor, agents that cause tumor cells to behave more like normal cells, drugs that keep tumors from invading normal tissue, and agents that control cell growth and enzyme production or action. Scientists also are working on gene therapies for CNS tumors.

With my type of tumor–a low-grade astrocytoma--my doctor says my outlook is pretty good. I'm hoping that in the next few years they'll have even better treatments for my cancer.

Research is underway on all types of brain and CNS tumors. In addition to developing new imaging techniques and treatments, scientists are working intensively to better understand the molecular and genetic changes that occur in CNS tumors. These discoveries will accelerate the development of better preventive and therapeutic interventions, and will improve our ability to detect CNS tumors and monitor their response to treatment

I can't help wondering what caused my brain tumor, but mostly I'm just trying to move ahead and make the most of my life.

The causes of CNS tumors are not well understood. Six inherited genetic syndromes have been associated with CNS tumors, but inherited genetic alterations are not believed to account for a large proportion of these tumors. Gene alterations that may lead to a CNS tumor can also be caused by environmental factors, but the evidence on most factors studied to date is inconsistent. One exception is that high-dose radiation used to treat brain tumors has been related to second CNS tumors in survivors undergoing this type of treatment. However, low-dose radiation from diagnostic x-rays and workplace exposures have not clearly been found to increase risk of CNS tumors, nor has exposure to low energy electromagnetic (EMF) or the microwave frequencies associated with cellular telephones. It appears that regular exposure to some categories of chemical agents (e.g., N-nitroso compounds, some pesticides) may increase the risk of CNS tumors, but there is still more research to be done in this area. Similarly, researchers are exploring whether exposure to certain viruses may affect CNS tumor risk. But the majority of people with CNS tumors do not have any of these possible risk factors.

Most people living with CNS tumors will have symptoms that may change over the course of their disease. An important area for further research is to learn how to help people cope most effectively with the physical and psychological impact of these diseases, and the possible short- and long-term side effects of their treatment.

This year, NCI convened a Progress Review Group on adult and childhood CNS tumors to assess the current state of knowledge and care for this diverse group of diseases, and identify research priorities for the future.

Note: This vignette is a composite of experiences.

People's Story:
Ovarian Cancer

My mother died from ovarian cancer when I was 17. By the time she went to the doctor about the leg pains and bloating, the cancer was already advanced.

Symptoms of ovarian cancer are often vague and may be ignored or mistaken for other illnesses. A woman may feel bloated or have general discomfort in the lower abdomen. She may have a loss of appetite or a feeling of fullness, even after a light meal. She also may experience frequent indigestion, gas, or nausea. A tumor that presses on the colon or bladder may cause diarrhea, constipation, or frequent urination. In some cases, fluid buildup around the lungs can cause shortness of breath. Contrary to common belief, unusual vaginal bleeding is a less common symptom of ovarian cancer.

This year, an estimated 23,100 new cases of ovarian cancer will be diagnosed in this country, and nearly 14,000 women will lose their lives to the disease. Ovarian cancer is the sixth most common cancer in women, and the fifth most common cause of cancer death among women. It has the highest mortality rate of all female reproductive system cancers.

Because of my mother's experience, I pay attention when I don't feel right. My doctor says that catching it early is the most important thing.

When we are able to diagnose ovarian cancers early before they spread outside the ovary they can usually be treated successfully. The five-year survival rate with treatment in the early stages is 95 percent. Unfortunately, only 25 percent of cases are detected this early, and survival drops sharply when ovarian cancers are diagnosed at later stages. For this reason, women and all physicians who treat women should be suspicious if any of the symptoms listed above persist.

We got a computer this year, and I've found information on the Internet about ovarian cancer. The trouble is, there are screening tests, but they're not very effective. It's over 50 miles from our farm to the hospital where the gynecologist is, but I'd make that trip any day of the week for a test that could tell for sure if I have cancer or not.

The lack of a reliable screening test has been major barrier to improving ovarian cancer detection and increasing survival rates. Routine pelvic examination, the standard screening method, misses one-third of even relatively large ovarian tumors. Two other screening tests for ovarian cancer are sometimes used. One is a blood test that measures levels of a protein called CA-125 that is produced by some ovarian cancer cells, and the other is transvaginal ultrasound imaging. However, because both tests have significant limitations and are costly, they usually are performed only if a woman has symptoms or is known to have an inherited risk for the disease. NCI's Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial (http://dcp.nci.nih.gov/plco) is currently exploring whether or not routinely using these two tests together might be more accurate and ultimately decrease the number of ovarian cancer deaths.

Recognizing the urgent need for better ovarian cancer detection methods, NCI has several exciting new activities underway. Intensive research is being conducted to find more accurate, simple marker tests for ovarian cancer. For example, some studies suggest that ovarian tumors may have unique secretions that, when detected, could signal very early ovarian cancer, or even pre-cancer. Several centers and laboratories funded under NCI's Early Detection Research Network (ERDN) (http://edrn.nci.nih.gov) are devoted to identifying such biological indicators of ovarian cancer that could be detected quickly, easily, and accurately.

In addition, because it is so difficult to obtain very early stage ovarian cancer tissue for study, researchers are working on designing mouse models to learn how this cancer develops. Recently, several mouse models for early epithelial ovarian tumors have been developed that show promise for uncovering the earliest cellular and related molecular changes that give rise to ovarian cancer. Work in this area has been greatly accelerated by the funding of four Special Programs of Research Excellence (SPOREs) dedicated to ovarian cancer research, and by collaborations with researchers in NCI's Mouse Models of Human Cancers Consortium, *In Vivo* Cellular and Molecular Imaging Centers, Cancer Genetics Network, and the Divisions of Basic Sciences and Clinical Sciences.

There are better treatments for ovarian cancer than there were when my mother was sick, but they still need to be improved.

Following surgery, women with ovarian cancer usually receive a combination chemotherapy that includes a drug containing platinum and a taxane such as paclitaxel (Taxol®). Recurrences may be treated with additional doses of these agents or with other anti-cancer drugs. New or improved treatments for ovarian cancer are being tested in clinical trials. For example, a recently reported randomized trial compared a combination of Taxol and cisplatin for treating advanced ovarian cancer with a combination of cyclophosphamide and cisplatin. After nearly four years of follow-up, the Taxol/cisplatin patients showed significantly improved overall drug response, progression-free and overall survival, and complete remission rates. Other new therapies under study include high-dose chemotherapy with bone marrow or stem cell transplant, other new chemotherapy combinations, treatments that block cancer gene products like the protein produced by the *HER-2 neu* gene – often altered in ovarian cancer – and a variety of other gene and immune system therapies, such as vaccines that help the immune system recognize cancer cells. In addition, laboratory and animal studies are underway to determine if lowering certain hormone levels in women treated for ovarian cancer will prevent the disease from recurring.

Since my mother had ovarian cancer, my risk for the disease is higher than average. My doctor says that if my mother, sister, or even my daughter has ovarian cancer, I am nearly three times more likely than other women to get it. So I'm going to be careful – I don't want my kids to lose their mother the way I did.

Five to 10 percent of ovarian cancers are believed to be caused by inherited mutations in the *BRCA 1* or *BRCA 2* genes, which also increase breast cancer risk. NCI is sponsoring further research into inherited genetic ovarian cancer risk through its Cancer Genetics Network, Cooperative Family Registries, and Clinical Epidemiologic Studies in Hereditary Breast/Ovarian Cancer.

NCI is committed to improving ovarian cancer prevention, detection, and treatment, and fully expects that the new ovarian cancer SPORES, which support innovative, multidisciplinary research approaches with the potential to have an immediate impact on cancer care and prevention, will be important hubs of progress against this disease. In 2001, NCI will bring together leaders in basic, clinical, and population research and the consumer community to assess the state of knowledge and identify research priorities to hasten progress in understanding, preventing, and treating ovarian cancer and other reproductive system cancers in women.

Up-to-date information on ovarian cancer is always available on NCI's Web site, CancerNet (cancernet.nci.nih.gov) to help women understand this disease and learn about advances in screening, risk assessment, and treatment.

Note: This vignette is a composite of experiences.